

Public Meeting
Matters Related to Protection of Human Subjects and
Research Considering Standard of Care Interventions
Wednesday, August 28, 2013
Hubert H. Humphrey Building, Great Hall

9:00 a.m. – 9:15 a.m.

Opening Remarks

Wanda K. Jones, DrPH
Principal Deputy Assistant Secretary for Health
U.S. Department of Health and Human Services (HHS)

HHS Panel

Jerry Menikoff, MD, JD
Director, Office for Human Research Protections

Kathy Hudson, PhD
Deputy Director for Science Outreach and Policy
National Institutes of Health

Robert Temple, MD
Deputy Center Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

9:15 a.m. – 12:00 p.m.

Presentations & Panel Questions

- 9:15 a.m. [Michael Carome](#), MD
Public Citizen (Washington, DC)
- 9:28 a.m. [Sidney Wolfe](#), MD
Public Citizen (Washington, DC)
- 9:41 a.m. [Alice Dreger](#), PhD
Northwestern University (Evanston, IL)
- 9:54 a.m. [Lois Shepherd](#), JD
University of Virginia Health System
- 10:07 a.m. [George Annas](#), JD, MPH
Boston University
- 10:20 a.m. [Charles Natanson](#), MD
- 10:33 a.m. [Vera Sharav](#)
Alliance for Human Research Protection (New York, NY)
- 10:46 a.m. [Elisa Hurley](#), PhD
Public Responsibility in Medicine and Research (Boston, MA)
- 10:59 a.m. [John Lantos](#), MD
Children's Mercy Hospital (Kansas City, MO)
- 11:12 a.m. [Benjamin Wilfond](#), MD
Seattle Children's Research Institute (Seattle, WA)
- 11:25 a.m. [Robert Danner](#), MD

11:38 a.m. [Nancy Kass](#), ScD
Johns Hopkins Bloomberg School of Public Health (Baltimore, MD)
11:51 a.m. Session wrap-up

12:00 p.m. – 1:00 p.m. **Lunch**

1:00 p.m. – 4:30 p.m. **Presentations & Panel Questions**

1:03 p.m. [Jeffrey Drazen](#), MD
New England Journal of Medicine & Harvard Medical School
1:16 p.m. [Peter Vasilenko](#), PhD
Alion HRPP Accreditation Services (Washington, DC)
1:29 p.m. [Steven Joffe](#), MD, MPH
University of Pennsylvania
1:42 p.m. [David Forster](#), JD, MA, CIP
WIRB-Copernicus Group (Olympia, WA)
1:55 p.m. David Magnus, PhD
Stanford University (CA)
2:08 p.m. [Carl D'Angio](#), MD
University of Rochester (NY)
2:21 p.m. [Jon Tyson](#), MD, MPH
University of Texas Health Medical School
2:34 p.m. [Michele Walsh](#), MD, MS
Case Western Reserve University (Cleveland, OH)
2:47 p.m. [Shawn Pratt](#)
Private Citizen (WV)
3:00 p.m. [Sharissa Cook](#)
Private Citizen (AL)
3:13 p.m. [Edward Campion](#), MD
New England Journal of Medicine
3:26 p.m. [Michael McGinnis](#), MD, MPH
Institute of Medicine (Washington, DC)
3:39 p.m. [Richard Platt](#), MD, MSc
Harvard Medical School
3:52 p.m. [Ann Bonham](#), PhD
American Association of Medical Colleges (Washington, DC)
4:05 p.m. [Robert Califf](#), MD
Duke University (Durham, NC)
4:18 p.m. [Session wrap-up](#)

4:30 p.m. – 4:45 p.m. Brief summary of comments submitted by 8/7/2013, by those who did not present today

4:45 p.m. – 5:00 p.m.

Closing Remarks
Wanda K. Jones, DrPH

MODERATOR [INTRODUCTORY COMMENTS]:

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Good morning, everyone.

Welcome to the Hubert H. Humphrey Building, headquarters of the U.S. Department Health of Human and Services.

We have over 200 folks registered to participate in person today and quite a number of folks indicating they're going to be on line but we don't have current numbers.

But we're thrilled we have gotten a response to this meeting that we have gotten.

It's truly an historic day to be in Washington and really when we set the date for this meeting back in the late spring, we didn't realize it was going to coincide with the great events out on the Mall today and the commemoration of the 50th anniversary of the march on Washington which everyone remembers as the reverend Dr. Martin Luther King delivering his I Have a Dream speech, though he wasn't originally the featured speaker.

But it's 50 years later now, and we're able to look back and look forward.

That event, some of you may have experienced firsthand, but we know it's also creating the today's events creating transportation difficulties.

So we're grateful that you came early, that you made it here, and plan to spend as long as you can.

I anticipate the major traffic issues are going to be the next hour or two getting ready for one o'clock events at the far end of the Mall and then up until about 5 or 6 p.m., so if you haven't looked at any of the notification sites about transportation and logistics today, just for your general awareness.

Today's meeting here at Health and Human Services...

This meeting is intended to help us through the Office for Human Research Protections to develop guidance that is related to informed consent and what constitutes the reasonably foreseeable risk in research that involves standard of care interventions such that risk is required to be disclosed to research subjects.

We know this issue is of critical interest whether you're in this room, listening via webcast, or for folks not able to participate in any way today but sent comments and definitely are going to be watching. This public meeting will hear all views on the topic at hand.

And we're here to listen.

I ask all of us to listen with open minds respectful of all points of view and respectful of time.

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Presenters: We'll get to your logistics in a second but presenters were notified of their allotted times and we want to ensure whether you're the third presenter or the 27th, that you have the same allotted time today.

So the agenda is very, very tight.

We have a count down clock up here that will be used to ensure that we keep on schedule.

Each presenter will have seven minutes and at seven minutes I'm going to start sending signals to presenters to wrap up if you are not indicating that you are wrapping up.

We intend to have five minutes of clarification questions with the federal panel. I'll have them introduce themselves in a moment.

So we really do want to respect all these points of view and ensure that in the fairest way with the time we have allotted that you honor our request to stick to your seven minutes.

We'll break for lunch at noon and reconvene at 1 p.m. We may flex a bit, then I'll also be probably needing to find a time during our morning and afternoon sessions for a brief comfort break for the panel.

For those of you in the audience: If you need to make a phone call, if you need to use the restroom, take that break as you need to.

So turn your cell phones off or put them on vibrate, or silent, or whatever.

If you need to go to outside the wall there or outside, outside to take your call, feel free to do so.

Remember when you leave this immediate area you must be accompanied by a federal badged escort.

It doesn't matter whether it's going to the restroom, nobody will watch you, it's not that kind of process, but it's an awkward building given the time we were built and the way we need to maintain security perimeter now in federal buildings.

So you do need an escort, restrooms.

If you decide to eat up stairs in our cafeteria on the 9th floor it's labeled PH, not Public Health, it's Penthouse in this building where there's a nice cafeteria.

You would need to be escorted.

Lunch options, many things around the Federal Center SW Metro station, in addition today is our Fresh Market out in front of the building in the white tent.

So there are food vendors with a variety of Asian, Indian, Louisiana, gumbo-type foods, barbecue, chicken, pork, beef, barbecue, vegetarian options, etc. out front.

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You don't need an escort out there and you'll come back through the front doors.

So it's under tents, there are seats there, there's seating so it could be a good option even if a little sprinkling midday.

If you want to understand some of the local options outside the building, just ask staff who are around.

So I have given logistics and you're wondering, Who the heck is she?

I'm notorious for not introducing myself.

But I'm Wanda Jones, Principal Deputy Assistant Secretary for Health in the Office of the Assistant Secretary for Health, and I am your moderator today.

The meeting is being streamed live, and will be archived for future viewing by sometime next week.

We never can be precise, when it will go up on the website but OHRP website www.HHS.gov/OHRP is where to look for the archived webcast.

We do expect to have a transcript of the meeting posted on OHRP's website by close of business tomorrow.

In addition, presentations and comments are posted online already at the website.

And look for the HHS announcement banner and click on Resource Page.

Follow the instructions on how to view submitted comments.

For those here today, we have two notebooks at the registration table with printed copies of all of the presentations and comments attending that for your review while you're here.

We do appreciate the more than 40 comments we have received to date.

We plan later this afternoon to review those that were received before the deadline of August 7th.

But comments have continued to come in and the comments docket remains open until September 9th.

So after today you may send additional comments, folks viewing may send comments.

They must be in no later than 5 p.m. on September 9th for consideration.

Again, that information is on OHRP's website, but you can also find the docket at www.regulations.gov and the docket number is HHS-OPHS-2013-0004.

Enter that in the search box, click the Comment Now box, many have already done this but for those viewing and those here, it's pretty easy to do.

Again, we very much appreciate the public comments, this process is intended to ensure that we get all views from those who have a view to offer on the questions at hand.

Now it's time to turn to my distinguished colleagues who agreed to serve on our panel today from our sibling agencies within the Department, and I would like to ask them to introduce themselves.

KATHY HUDSON:

My name is Kathy Hudson, Deputy Director for Science Outreach and Policy at the National Institutes of Health.

JERRY MENIKOFF:

Jerry Menikoff, Director of the Office for Human Research Protections, part of the Office of the Assistant Secretary for Health.

ROBERT TEMPLE:

Bob Temple, FDA, Deputy Center Director for Clinical Science, Center for Drug Evaluation and Research.

MODERATOR:

Terrific.

Thank you.

So now it's time to get started.

Presenters you were notified of your time and our first three presenters: Michael Carome, Sidney Wolfe, Alice Dreger; next Lois Shepherd, George Annas, Charles Natanson; the next three Vera Sharav, Elisa Hurley and John Lantos; and then the last three in the set: Benjamin Wilfond, Robert Danner, and Nancy Kass.

As I said sort of getting a sense of we need to take a break at the 10:30 to 11:00 point.

We'll just go with it.

We may not need one, we may proceed on and speakers you won't be penalized.

Trust me, I'm from the government.

Right?

So, Michael. Are you ready?

I have a clicker for PowerPoint slides and I will show you, so simple I can use it!

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PRESENTER: MICHAEL CAROME

MICHAEL CAROME:

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Good morning.

The most important take home message for OHRP today is that the obvious deficiencies in the SUPPORT study consensus process signal an urgent need to strengthen informed consent for human subjects research, not weaken it as some in the community are advocating.

It's remarkable and disturbing that the pretexts for this meeting are based on two major fallacies. The first is, the SUPPORT study is a representative example of research involving intervention that are used at standard of care treatment in the non-research context. It is not as review of the protocol- related documents will show.

Let me highlight just a few of the SUPPORT study's many complex experimental interventions that cannot be considered standard of care treatment in the non-research context.

Relying on a flip of a coin to make life and death medical decisions independent of subject's clinical status or need is not standard of care. Attempting to maintain oxygen saturations within a narrow high or low range combined with a masking procedure using display either falsely low or falsely high oxygen readings depending upon experimental group assignment was not standard of care.

The use of the falsely reading pulse oximeter represents an extraordinary deviation from standard of care in a non-research setting particularly since oxygen saturation levels play a role in many important clinical decisions related to the respiratory support, such as, whether to intubate or extubate an infant.

The stated purpose for using the altered pulse oximeters was to have a blinding procedure to avoid bias.

However, the unstated and more important purpose was to force the medical teams caring for the premature infants to consistently target the assigned experimental oxygen levels and achieve separation between the two groups.

This matching was considered essential to minimize co-intervention and contamination by bias of neonatal care providers.

Cole, et.al comment in a paper discussing the rationale behind the design of the SUPPORT, BOOST2, and Cox studies reflected an awareness that if medical teams caring for the study infants were given accurate oxygen information they would not maintain oxygen levels within the range stipulated by the research protocol.

This is a clear acknowledgment that the experimental target ranges were not consistent with standard of care interventions in the non-research setting.

The study CPAP experiments included an experimental group that did not receive standard of care.

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The treatment, i.e., experimental group received early CPAP with strict criteria for intubation and extubation designed to force babies off ventilation versus the control group which received similar to standard of care interventions including early intubation and surfactant which have been shown to be life saving, particularly in infants at 24-25 weeks gestation plus conventional ventilation and criteria for intubation that was considered standard of care.

In a 2004 presentation describing the SUPPORT study CPAP intervention the investigators noted the following.

These CPAP intubation criteria are more severe than have been used in any trial and as far as we can tell more severe than used in most network centers. The CPAP group clearly did not represent standard of care treatment.

Finally there was a complex interaction between the oxygen's experimental use of falsely reading pulse oximeters and the experimental criteria for deciding whether to intubate or extubate an infant in the experimental CPAP group, as shown in the protocol excerpts here. It is notable that these criteria are based in part on false pulse oximeter readings, something that would never occur in standard of care.

It is notable these criteria are based, in part, on false pulse oximeter readings.

The investigators recognized that these criteria were not consistent with standard of care as they stated the following in the protocol.

CPAP infants who require intubation three times for any criteria will have subsequent treatments including subsequent extubations and re-intubations performed using standard of care.

This addition is to prevent such infants from being exposed to further protocol driven intubations and extubations.

Thus the support study clearly involved many interventions that deviated from standard of care in the non-research context.

Every infant in the study received experimental interventions that were not standard of care.

The low oxygen CPAP group received the most extreme combination of experimental intervention, the low oxygen target, management with miscalibrated pulse oximeters, CPAP, and severe criteria for intubation-extubation designed to force the infants off ventilation.

The second fallacy on which the pretext of this meeting is based is we have entered a new area of human subjects research that involves studies comparing different treatments that are used as part of standard of care or usual clinical care treatment in the non-research context.

And as a result investigators and IRB conducted and reviewed the SUPPORT trial and similar studies are justifiably unsure how to apply the requirements of the human subject regulations regarding informed consent.

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This fallacy must be rejected.

Randomized clinical trials comparing different interventions that have been used in treatment in the non-research context have been conducted for many decades and claims of ignorance regarding how to apply the regulations to such research ring hollow.

The history of human experimentation over the past century is filled with victims of unethical research conducted without adequate informed consent.

When outrage over revelation of unethical research reached a crescendo in the early 1970s, Congress finally passed a law requiring HHS to ensure the protection of human subjects.

The resulting regulations were implemented nearly four decades ago.

Now in the wake of disclosures about the unethical conduct of the SUPPORT study there appear to be a real possibility that these disclosures will result in weakening of human subject protections particularly with respect to implementation of the ethical principle, respect for persons to informed consent.

Soon after OHRP's findings regarding SUPPORT came to public attention a group of individuals within the medical research establishment launched a well orchestrated attack against OHRP in defense of the SUPPORT study.

Leading this effort has been the editors of New England journal of medicine, the NIH director and many researchers and bioethicists with close ties to the SUPPORT study at NIH.

Many critics of OHRP's actions have sought to blur the line between research and clinical care and appear to view the process of obtaining informed consent as an unnecessary impediment to conducting clinical trials and advancing medical knowledge.

They want to change the rules to satisfy their research needs at the expense of subjects' rights. The fact that this meeting is occurring reflects as tremendous influence that NIH which approved the SUPPORT study and spent nearly \$20 million on it has wielded in an effort to undermine OHRP's authority and reverse OHRP's findings.

MODERATOR:

Your seven minutes are up.

MICHAEL CAROME:

In conclusion these efforts to weaken human subjects protections must not succeed.

Many in the bioethics and research communities agree that deficiencies in SUPPORT study consent forms are obvious and OHRP was correct in its findings.

As a Nature editorial said last week no matter the thorniness of the issues raised research is still research in whatever context and duty to protect human subjects must remain paramount. OHRP staff created this transcript from the video captions by correcting transcription errors and identifying the speakers.

In closing as Dr. Menikoff said about the SUPPORT study, this should never happen again.

Unfortunately even now it is happening again.

Thank you.

MODERATOR:

Thank you.

Let me turn to our federal panelists, FDA.

ROBERT TEMPLE:

Let me just ask about the -- this was a factorial study and one factor was what oxygenation level patients would be sent to, which was the major area that OHRP criticized.

Apart from what physicians were supposed to do in the event of people having difficulty do you think there was a problem with comparing the high oxygen level and low oxygenation level as a perfectly reasonable thing to explore if there was uncertainty about it and what do you think people should have been told about that part of the study?

MICHAEL CAROME:

There's a lot to say in response to that question.

What we had essentially was two experimental groups getting care that was altered with respect to their oxygen therapies were replaced randomly, subjects on either side of the extremes of the usual range of oxygen therapy, irrespective of clinical factors that may be taken into account doing that and we combine that with pulse oximeters that blinded the entire medical team to the care of these infants in terms of what oxygen they were on and that combination procedures clearly exposed these infants to serious risk.

What should have been disclosed to the parents were those serious risks including the risk of death, the risk of eye injury and blindness, the risk of brain injuries, depending upon individual factors and what group the babies were in.

There should have been a much clearer disclosure of how the research was altering the care of these infants compare to care they would have received had they not been in the trial.

In general the consent forms failed in many regards across all the centers.

MODERATOR:

NIH?

KATHY HUDSON:

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Thank you.

At the time the study was initiated you argue that the parents should have been informed that in the two arms two oxygen arms of the trial parents should have been informed of differences an increase risk of death.

What were those in your evaluation of the literature and what should parents have been told about their increase risk in those two arms increase risk of death? And noting that of course these babies were extremely vulnerable within extremely high mortality rates, something in the order of 25 to 33%.

MICHAEL CAROME:

We agree, yes, these were critically ill babies with high baseline mortality rate and doing things to alter care for the purpose of experiment could have altered various outcomes including death, brain injury, eye disease.

We know from earlier studies dating back decades that oxygen is life saving.

If these babies have undeveloped lungs if you don't give them oxygen the death rate will be much higher than the 20% you noted.

We also know if you give 100% oxygen all the time to the infants that they will have a higher rate of eye disease retinopathy of prematurity.

There are offsetting risks, death on the one hand, if you don't give enough oxygen, eye disease if too much for too long.

That was generally known.

This research was trying to see if we could find medium sweet point where we could lower the risk of eye disease without affecting the death rate.

But that indeed was unknown, they were trying to answer that and it was highly conceivable that giving not enough oxygen to low group would increase death rate for some infants and the high oxygen group could receive higher oxygen than they would have otherwise received had they not been in trial and that could have included eye disease.

Those risks were reasonably foreseeable and should have been disclosed to the parents.

MODERATOR:

OHRP?

JERRY MENIKOFF:

I would like to thank Dr. Carome, no questions.

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MICHAEL CAROME:

You're welcome.

ROBERT TEMPLE:

Can I ask another?

MODERATOR:

One minute.

ROBERT TEMPLE:

So the consent form actually at least somewhat referred to the possibility that higher oxygen could cause ophthalmic disease. But I have to agree that it did not say what the downside was, which of course was part of what was being looked for, it was part of the primary end point. Is that your principle criticism?

MICHAEL CAROME:

It would be one of many criticisms that we have. You are correct.

A couple of the consent forms noted in the risk section that there's a risk of eye disease, some in the background discussion noted we are trying to figure out whether eye disease might be altered with respect to oxygen levels.

Many of the benefit sections of the consent forms noted that a possible benefit was lower likelihood of developing eye disease.

If that's the case, that was not an unreasonable thing to disclose, the counter to that is there were risks depending which we end up having more eye disease.

MODERATOR:

Thank you.

PRESENTER: SIDNEY WOLFE

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SIDNEY WOLFE:

Extending beyond what Dr. Carome said, standard of care research is a misnomer for an experiment. Testing comparative risks of a subunit of a broad range of what may itself be a standard of care is really conducting an experiment, with subunit risks certainly differing from those of the broad range,

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otherwise why would there have been any point in doing the experiment? Subunits themselves cannot be standard of care.

The main source of conflict precipitating this meeting are contrasting views of whether interventions in SUPPORT and similar studies are more like experiments or more like existing standards of care.

Another way of looking at this dichotomy is the dichotomy between foreseeable risk of an experiment and standard of care or to continue the dichotomy between obligation of researchers as researchers and obligations of clinicians taking care of patients.

In a letter signed by a number of people who will be presenting this meeting, researchers involved in the study, researchers not involved in the study, ethicists, to the New England journal, they confirmed the stance on this conflict.

Saying these two saturation targets were consistent with standard of care, conclusion -- they stated the conclusion of OHRP that the study's experimental evaluation of these otherwise routinely used oxygen saturation levels, in other words the implication is each of these two ranges were routinely used, which I doubt seriously is the case, separately. exposed subjects to additional risk is not supported by the evidence.

This again was from Dr. Cole, whose paper referred to by Dr. Carome. This actually said, in designing the study we need to do it because of important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen intentions.

I think one of the things that most illuminates to me part of the answers to the question that Dr. Temple and Dr. Hudson asked is, what should you have told them?

The answer instead of being looking back at what you should have told them, you can look at a consent form that actually did tell them these things.

None of the U.S. consent forms mention the risk with regard to use of lower oxygen levels, in contrast, 2005 version of consent form in New Zealand BOOST study, which was obtained by OHRP and sent out in a letter to all the investigators two and a half months ago, this is what that consent form said to the patients who were being considered for participation.

Too low oxygen in the blood, for long periods may increase the risk the baby will not survive or contribute to poor growth and damage the brain cells and lead to developmental problems.

The aim, the purpose of the study, something important to state in the informed consent, the aim of the study is to determine within the range of oxygen saturation currently being used (85 to 95), whether targeting the lower end of this range, (85 to 89) compared to upper end of the range (91 to 95) is safe and effective in reducing serious vision and lung problems without increasing mortality or neuro-developmental disability.

So this is something used in New Zealand, I doubt whether the babies there had any different resistance to low oxygen or high oxygen as they do here.

But they thought it important and at the end of this OHRP letter, they said had U.S. investigators included something like that, we would not have criticized them for omissions with respect to the dangers of low oxygen.

The underlying principle behind arguments opposing full informed consent in such experiments is that it is necessary and a mechanism whereby this can be accomplished is inadequate informed consent to blur the line between research and standard of care to facilitate more consent and participation.

The origins of this are not recent. 20 years ago, in a letter in the British medical journal by noted British neonatologist Dr. Mode she said though it might be argued parents have a right to know about all aspects of their baby's care, this would mean in many instances distressed parents were forced to make decisions they would not normally asked to make.

In other words, they would be given information about the experiment versus what they would otherwise get and that makes it difficult. And no doubt it's difficult but it is argued by us that they do have a right to know.

Back 30 years ago the issue of therapeutic misconception arose when participants in several studies were found to be unaware of participating in study and receiving personalized care in the clinical setting.

They said then that research participants' failure to recognize how personal care, or the obligation of physicians to make medical decisions, may be compromised by research procedures.

More recently, this concept was studied in 25 different experiments on 225 people that agreed to participate and a third expressed inaccurate beliefs regarding degree of individualization of their treatment as a result they may have failed to clearly appreciate the risk benefit ratio of research project to which they're being asked to consent.

Blurring the distinction between standard of care and experiments such as SUPPORT is fostered by inappropriate inaccurate portrayals of experiments in the consent forms.

To look at the consent form, we examined 15 of 22 literally referring to each of the separate arms to which someone maybe randomized says it's standard of care.

Further, in terms of the risk, 20 of the 22 consent forms failed to identify retinopathy of prematurity or brain injuries as a result of, as a risk of research and none mentioned risk of death for the oxygen experiment as I mentioned earlier.

This is paper published a couple of years ago people who do research --

MODERATOR:

Time is up. Please wrap up.

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SIDNEY WOLFE: I will summarize the final slide then.

Other remedies to the serious problem of misinformed consent or therapeutic misunderstanding must include enhancing surveillance and authority to enforce existing regulations, not weakening the surveillance authority or the regulations.

To weaken these, the authority and regulations protecting human subjects, would be to sacrifice critical informed consent dependent autonomy of patients' decisions about whether they participate in research by deferring to researchers autonomy to conduct trial.

MODERATOR: Thank you.

Panelists, OHRP.

FDA.

ROBERT TEMPLE:

One of the thoughts I had as I was reading this material is that one way to conceivably inform patients would be to be very explicit about what the end points of the study were.

Which was not in the consent form. I know it's hard to translate these things sometimes. Do you think that an appropriately worded statement well, we're looking at eye disease and we're looking at pulmonary disease and death and that's what we're going to look for and we don't know which, blah, blah, blah.

Would that do the job?

SIDNEY WOLFE:

I think what I read from the New Zealand consent form really does that in terms of the oxygen part of the experiment.

So the purpose of the experiment is to see whether we can, as Dr. Carome referred to, find somewhere within what is the range of 85 to 95, that may be better.

Among other things, the experiment should have had a control group that was actually the real standard of care.

But yes, if they had said the purpose of the experiments is to see whether we can reduce the risk of eye damage at a higher group and reduce the risk of death in the lower group by looking at these two groups, obviously people depending on which group they're randomized to may have different results in terms of death or eye disease.

Yes. Going in that direction would have been much more informative obviously back in 2005 people in New Zealand got it with respect to oxygen so it wasn't something that was unknown, unimaginable, based on unforeseeable risk.

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In New Zealand they thought there were foreseeable risks, they felt obligated to inform parents about the foreseeable risk.

MODERATOR:

NIH.

KATHY HUDSON:

No questions, thank you.

MODERATOR:

No other questions from the panel. Okay. Thank you very much.

PRESENTER: ALICE DREGER

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MODERATOR:

Alice Dreger, thank you for being ready.

ALICE DREGER:

These remarks are jointly authored by Susan M. Reverby, Marion Butler McClean Professor at Wellesley College in Massachusetts.

Professor Reverby is unable to join us today.

I expect you are familiar with her work including her award winning books on the Tuskegee Syphilis Study and her discovery of the Public Health Services' 1946 to 1948 sexually transmitted disease study in Guatemala.

Professor Reverby and I speak to you today as historians seeking to provide historical context and to make recommendations based on the long view.

Because of time limits we present orally only a portion of our written analysis.

OHRP was right in its findings on the SUPPORT study.

As stated in the letter we signed with 43 of our colleagues to the New England journal quote: "The Informed consent documents that were...that were used were seriously inadequate" unquote.

Please note: Using the phrase "standard of care" whether in clinical care or clinical research, does not exempt a physician from clearly explaining risks before obtaining consent.

Here as so many times in the history of American medical research, the consent process failed.

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Now we would note that the successful pressure put on OHRP to pull back on enforcement represents a frightening and dangerous precedent.

Yet that is what is new here.

Not the essential kind of research, nor unfortunately the failure to obtain informed consent.

As historians we can tell you there is nothing magically different about today's technologically advanced multi-center clinical trials like the SUPPORT study that makes them exempt from the code and regulations that are already devised.

Existing OHRP regulations are absolutely adequate for the management of trials involving commonly used medical interventions as well as for trials like SUPPORT.

We are not in a new era, ethically speaking.

We are in fact here again to have the same conversation we've been having for generations about failure to obtain appropriate informed consent.

It's a conversation worth having but we should not pretend it is new.

Almost 50 years ago, in 1966, Henry K. Beecher published his now famous review in the New England journal called "Ethics and clinical research", which showed that ethical problems within American medical research appeared endemic.

Given the problems with risk disclosure in the SUPPORT Study's consent process we fully expect that if Beecher were re-doing his study today he would find many problematic contemporary studies, including the SUPPORT study.

This is exactly why we need OHRP's enforcement to stand and why we continue to need external eyes on research trials.

Beecher's analysis suggested that the etiology of the problem laid in a skewed professional milieu that today has become even more problematic.

Although individual medical researchers are motivated by a beneficent desire to preserve health and save lives, what is rewarded in the medical research system is ever more scholarly production, not nuanced ethical behavior.

Indeed, in today's academic climate researchers who attempt to be ethically meticulous may find themselves effectively punished through delays, lower enrollment and thus failure to compete.

In short, the system is set up to allow these ethics problems to keep happening; it may even promote ethical short cuts and missteps.

If ethical short cuts and missteps go unpunished, if OHRP fails to enforce findings of wrong-doing, what external incentive is there to be ethically meticulous other than the fear of lawsuits?

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Make no mistake, we are enthusiastically in favor of good clinical research even on premature babies, but such research which has the potential to benefit the whole of society cannot be done at the expense of the rights of the vulnerable individuals who are used as subjects, and in this case the rights of their parents as well.

Some have claimed that the move toward more evidence-based medicine or toward a so-called learning healthcare system, in which essentially every patient becomes a subject, requires a system where the line between patient and research subject becomes blurry.

We strongly object to this idea and we warn you that this type of reasoning has been used again and again as a way for researchers to justify poorly consented risky research on unsuspecting subjects who thought they were just patients.

Although we are not saying that the SUPPORT Study is akin to the Tuskegee study, and we would discourage over-using the Tuskegee Study as a metaphor, we should understand that the Tuskegee study was in many ways understood to be a kind of standard of care research because the researchers thought the men in the study were not going to get adequate treatment for syphilis anyway.

But the road to better-informed evidence-based medicine ought never be paved with the bodies of ill-informed subjects.

We cannot allow physicians to slip into a mode where they fail to remain vividly conscious of the difference between patients and subjects.

As Beecher understood, well-intentioned researchers - often people at the tops of their field - have been responsible for much of the ethical mischief committed in medical research.

Ethical mistakes happen not because most researchers become Nazis deployed by an evil state or greedy researchers employed by big Pharma or self-centered egomaniacs.

Ethical problems happen because of tremendous intrinsic and extrinsic pressures on American clinical researchers to produce good science.

Until medical professionals realize that the road to hell is paved with good intentions, until they truly believe that good people can unthinkingly do bad things in everyday work, we will continue to see the same mistakes happening.

We will continue to ritualistically meet like this to express shock, failing to see the irony of how a cathartic event such as today's hearing of possible scandal and punishment keeps the same dangerous system in place.

Until we see how we have created an environment that fosters ethical mistakes and now openly resists enforcement when mistakes are found, the same problems will keep arising.

We make the following recommendations and conclusions.

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The case of SUPPORT should not be used to discuss research on interventions that are commonly understood to be a standard of care, because several of the experimental interventions would have to be called clinically peculiar if not clinically non-existent. The use of the phrase

"standard of care" in clinical medicine or clinical research does not exempt a physician or a researcher from an honest discussion of risks with patients and subjects as part of the consent process.

OHRP and HHS should require extraordinary proof before accepting any claim that today's forms of research require revised regulations, or new interpretations of regulation.

The existing regulation is adequate and should not be weakened in the name of promoting science and promoting patient care.

Vigorous enforcement of existing regulations is needed and should be supported, not hampered.

The successful political pressure from NIH and researchers that has forced OHRP to back off its enforcement actions suggests that any revision of existing regulations at this political moment may well result in weakened protections for subjects.

Parents who agreed to enroll their children in the SUPPORT Study should be informed of OHRP's findings.

The SUPPORT trial should be understood to be another classic case of failure of informed consent committed by well-intentioned eager researchers focused on the greater good, driven by a problematic system.

We should all acknowledge that the system is set up more to foster than to prevent these kinds of ethical failures. Enforcement in cases of wrong-doing and active rewards for meticulous ethical behavior will be critical to producing ethical behavior.

In conclusion, we do not think that any bureaucratic system can perfectly prevent more cases like this from happening.

The only real protection would involve a combination of extreme humility, the constant attention of the uninvolved, and a genuine willingness on the part of academic researchers and administrators to lose in the research game, if losing is what it takes to put ethics first.

MODERATOR:

Time up is up.

ALICE DREGER:

Thank you.

MODERATOR:

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NIH?

KATHY HUDSON:

Thank you very much for your comments.

So you argue that the SUPPORT Study should not be used as a sort of a center point for discussing informed consent for standard of care research.

But I think you would agree that it's important for us to continue to do research on what is now the standard of care in order to improve that so that we have a better understanding of the optimal interventions versus the less optimal interventions.

So if you don't believe that the SUPPORT study should be used as a centerpiece for discussing the standard of care do you agree that we have a need to talk about what are those issues for participants and researchers as we seek to improve the standard of care through additional research?

I'd be interested in your talking a little bit more about that blurry line between patient and participant and how we make it distinct.

But I do believe we should encourage as many patients as possible to be research participants and actively involved as participants, and so I would be interested in a little bit more of your thoughts on that.

ALICE DREGER:

Thank you for your question.

I certainly support and would encourage research on interventions that are commonly used in the clinic.

We all know that historically speaking medicine has not been evidence-based, evidence-based medicine is a relatively new phenomenon.

And a lot of what goes on in clinical care - obstetrics would be a good example that I have written about personally - what is happening is not based on good evidence.

So absolutely we need those kinds of studies.

I would shy away from calling this standard of care research because I think that phrase ends up making people think that somehow what you're doing doesn't add any risk, and you're sort of getting out of jail free in that sense.

I would prefer to think of it as interventions on commonly used...studies on commonly-used interventions.

And certainly we can do that and manage to explain to parents or subjects in other cases, that when you go into a randomized system, it ceases to be the case that your physician is individualizing care for you.

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It may be the case that the individual care is not very evidence-based, but in the cases when you are not in research your physician is attempting to individualize your care; as soon as you go into a randomized system that ceases.

MODERATOR:

OHRP?

JERRY MENIKOFF:

Thank you for your comments.

And if I can sort of pick up on what Dr. Hudson was talking about.

If we imagine - and many of the other commentators are sort of giving these in examples - there might be scenarios in which we're comparing two things that actually we don't have any supposition in terms of differences between them and perhaps you think there might be situations in which we basically these are in fact minimal risk studies because there's a much bigger picture in terms of scenarios that are very, very different than the fact pattern that started this discussion, and just sort of your thoughts...

ALICE DREGER:

Yes certainly. I'll give you an example from my own life: I use a cream for my rosacea. It's completely not studied for the use that I'm using it for.

I would love to be in a randomized controlled trial that actually tested this and told me what I'm doing to my body - whether or not this is safe, whether or not it's effective.

We lack that in all sorts of places so certainly this kind of research would be very important but I think we shouldn't slip into the system where we think just because it's already being used in a clinic there's very little risk involved and we don't have to have the consent discussion. We always have to....

One of the good things that could happen out of this, right, is that the kinds of consent discussions that ought to be happening in clinical care and are not could be forced into discussion by virtue of adding research to the mix.

So the research attention to informed consent might improve the attention to informed consent in clinical care.

MODERATOR:

FDA?

ROBERT TEMPLE:

Well, for reasons that you've given the fact you're studying it means that you think there might be a difference, otherwise you wouldn't bother to study it and there wouldn't be any purpose in it.

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I guess I've always thought standard of care was used to explain why it's reasonable to study this treatment, a lot of people believe in it, et cetera, et cetera.

But what you're saying, I think if I understand you is that the fact that it's standard of care doesn't mean there couldn't be important differences and this illustrates that because there were potentially important differences being looked for, on eye disease and lung disease and survival.

So whether people call it standard of care to support the idea that these are widely used, is the remedy to make sure that you do say what you're looking for and what the downsides and upsides might be?

ALICE DREGER:

And existing regulations say to do that.

They tell you to tell people the purpose of the research, they tell you to tell them what kinds of risks you're interested in so it would be reasonable in these cases to follow the existing regulations.

ALICE DREGER:

Thank you very much.

MODERATOR:

Thank you.

PRESENTER: LOIS SHEPHERD

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LOIS SHEPHERD:

My comments address three conceptual problems I see embedded in how the topic for this meeting has been framed which asks how an IRB should assess risk of research involving randomization to one or more standard of care interventions.

Though I will focus on these broader conceptual points today I have separately submitted written comments respond to each of the specific questions contained in public meeting.

First it –is not clear what the term standard of care intervention means, nor is there reason to assume so called standard of care studies merit ethical treatment.

In some usages among consent forms in the SUPPORT study and some of the commentary defending them the term standard of care suggests the participants in study will receive the same treatment. They will receive outside the study.

This portrayal promotes the view that in a study like SUPPORT there is no difference between clinical care and research and thus no risk to research participation.

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But this can not be true in studies that randomize human subjects to two or more different interventional arms.

Many subjects in studies must as logical matter be receiving treatment that differs from the clinical care they would otherwise receive.

For example in the SUPPORT study a baby in NICU that normally targeted the higher oxygen saturation level had a 50% chance of being assigned to the lower level.

All of the babies in NICU that routinely targeted a mid range level say 88 to 92% oxygen saturation received by virtue of being in the SUPPORT study care that was different from what they would have received were they not in the study.

If treatments are different, different in ways important enough to study, the risk and benefits of the treatment are potentially different.

This was true in the SUPPORT study where infants assigned to lower oxygen level had a possibly increased risk of death compared to infants assigned to higher level.

If these infants were cared for in a NICU that usually targeted the higher oxygen level they did in fact through enroll in the study face an increased risk of death from that aspect of the study.

Even if they may have benefited from other aspects.

This risk was reasonably foreseeable as determining its existence was the very purpose of the study and should have been disclosed to parents rather than obscured in language describing the study involving quote standard of care end quote treatments that posed no predictable increase in risk for babies enrolled.

I take some defenders of the SUPPORT consent form to understand a standard of care study as meaning, not that participants will receive the same treatment they would have outside the study but that the study is comparing two or more interventions commonly used and within the bounds of good medical practice.

Parenthetically if that's what it means then SUPPORT study doesn't fit that definition either even if we focus on oxygen saturation targets.

But even if the SUPPORT study compared interventions commonly used that does not answer the question what should be disclosed to participants.

In the United States people have a legal right to choose whether to participate in clinical research or receive clinical care from physicians who have a duty to put medical interests first.

Unless they're told the differences between the care they would receive outside the study and the care they would receive in it, they cannot exercise that right by making an informed choice.

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Standard of care is not currently a term used in regulations nor should it be. Talking about standard of care studies is an inappropriate shortcut that obscures consideration of fundamental elements of ethical research.

My second concern is questions posed for this meeting focus exclusively on understanding risk.

While there's a tendency for informed consent forms to be divided into discrete and rigid disclosures, for example, risk, the right to withdraw, et cetera, it is helpful to think less about categories of disclosure and more about the purpose of disclosures.

That purpose is to enable potential subjects to make informed choices about whether to enroll in a study.

The current regulations require disclosures about more than risk.

They require among other things explanation of the purpose of the experiment as well as procedures being studied.

All these disclosures work together.

Isolation of risk makes it easier to lose sight of the goal of the consent documents and to get lost sparring over whether a particular risk is potential or uncertain or foreseeable whether risk is with randomization or additional to risk of routine care.

I would suggest that it would be more helpful to adopt a transparency model of consent for research similar to the approach Howard Brody advocated for informed consent processes in clinical care.

Transparency model would aim to make transparent to potential subjects the thinking of investigators.

What do they think they know, what is commonly believed, what exactly are they studying why did they choose the study design?

Had SUPPORT investigators been transparent in the consent process parents would have been more fully informed about risk and potential benefits to research participation for their subjects, for their infants.

Third, some of the questions posed in the public meeting notice about waiver of consent suggest HHS may consider revising or reinterpreting regulations to weaken existing protections for human subjects.

It's important to remember that the common rule is merely an extra layer of protection for human subjects.

Human research subjects have legal rights to bodily integrity and self-determination that derive from other sources.

Common law, state statutes, and in some instances Constitutional law.

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These are not affected by HHS requirements for federal funding of research.

What this means is that the research community understood broadly here to include investigators, IRB, funding agencies, bioethicists do not get to decide matters for the rest of the country.

It is not that their power and would ultimately be a disservice to the research community to mislead members to believing merely following the federal regulations, especially if they're watered down, would insulate them from liability or satisfy their obligations under the law.

In conclusion, I urge any guidance that might emerge from this process, one, avoid creating new rules for research that purports to study standard of care interventions; two, consider ways to make investigators thinking more rather than less transparent potential subjects and three honor and support individuals existing rights to bodily integrity and self-determination.

Thank you.

Thank you.

MODERATOR:

To the panel, FDA.

ROBERT TEMPLE:

No questions.

MODERATOR:

OHRP.

JERRY MENIKOFF:

I would like to thank Professor Shepherd both for your comments now and useful discussion of this issue elsewhere.

At a point we discussed earlier, if we move from this fact pattern and toward a fact pattern many are discussing let's assume we're comparing two drugs where there's at the outset of the study no particular reason to think there's a difference but we want to study it and see if there's a difference, the risk as far as you're aware are similar likely benefits are pretty similar, how different would that study be in terms of how to be treated in the rule?

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Clearly this is a big issue in terms of drawing lines as we move forwards.

Curious on your thoughts.

LOIS SHEPHERD:

Right.

In a different scenario you were using commonly used interventions, you couldn't say it was minimal risk because you didn't know what the risks were.

If the interventions have an important effect on the health of the participants you would want to disclose what the -- those effects are.

Those can be risks and benefits.

And put your study as potential difference between those risks and benefits then those would be reasonably foreseeable because you're studying them and those would need to be disclosed.

So you can't say that any difference is going to be minimal because they're uncertain.

If the interventions themselves carry risk, any difference between them that might be shown, which is what you're looking for, which justifies the study will have significant impact upon the health of an individual.

JERRY MENIKOFF:

You're not assuming -- presuming any difference at the outset.

Your point is that it's the unknown differences you consider making more than minimal risk.

LOIS SHEPHERD:

Right.

You're not assuming but that's what you're studying.

So you would have to explain what the usual care was and what the risk of that intervention were.

And then you would have to explain what the intervention -- research intervention is.

And how those might differ with respect to the outcomes.

With the study.

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Thank you.

MODERATOR:

NIH.

KATHY HUDSON:

No questions.

Thank you.

MODERATOR:

FDA.

ROBERT TEMPLE:

Discussion of minimal risk interested me. We think about a trial of a new drug versus placebo we never believe any new drug has minimal risk.

We think all drugs have certain risks but comparing the two things the question changes.

If you're comparing two cancer drugs of course there's risk of the drugs, they're all toxic as can be but what you're interested in here is potential difference between the treatments and that's the risk you're thinking about.

So you can imagine in some cases two symptomatic treatments for pain or something you might in some circumstances might you conclude that the study had minimal risk because you -- none of these represent real risk.

Is that -- does that seem possible?

LOIS SHEPHERD:

I would have to get more detail on what you're talking about but seems to me if there is a drug for example for which there are certain side effects or suppose some intervention where there's risk of death, and we don't know, we don't know what the difference is between the usual care and then

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whatever the new intervention you have to explain we don't know but that's what we're studying, we're wondering if there's a difference between how these things will affect you for example in the SUPPORT study, mortality, eye disease, lung disease.

Just because you don't know whether there's a risk, if the intervention affects the health of the individual in a certain way, any difference in that is going to be important to the individual to know about.

So I think part of the problem here is we're thinking about categories like risk and is there a long list of death, Eye disease, instead of this idea of having your thinking transparent, we don't know what the effect is on eye disease of this intervention.

This is what we're studying.

There may be increase risk in this arm, there may be a decrease risk in this arm.

But we don't know

ROBERT TEMPLD:

That could depend on differences you were planning to look for.

In this study, yeah you're looking at important things.

If you were comparing two antidepressants and you see which caused more nausea, you might conclude it's -- could you some of those cases conclude that the comparison was minimal risk because the difference between the treatments is unlikely to be of consequential risk.

LOIS SHEPHERD:

If nausea is not a minimal risk, then.

The difference in nausea couldn't be a minimal risk, a potential difference in them.

I go with what the harm -- I focus more on the harm and any -- if the harm is significant enough that it should be disclosed, the difference in the rates of harm would not be minimal.

MODERATOR:

I was beeping myself with my timer.

I'm sorry.

So Okay.

MODERATOR: I was getting into that discussion listening.

GEORGE ANNAS:

It's a privilege to follow Lois and Alice and my own -- also speaking behalf of colleagues at the Department of Health Law Bioethics and Human Rights at Boston University.

Leonard Glanz and Michael Grodin I am not speaking for the university obviously.

And I have more or less been a non-participant observer in this debate over the last few months.

I have observed that how you feel and talk about it is based where you're coming from.

If you come from a view trying to protect research, trying to encourage research, coming from a view of research institution, or coming from a view of protection of research subjects.

So I don't want to comment though they're directed at SUPPORT.

I want to comment on that.

Over the over arching things that I think we can agree with, maybe not but think we can, I want to mention the 50th anniversary of March on Washington.

And I don't think this meeting can go by without acknowledging that disparities research is a major part of what NIH is doing and that though SUPPORT didn't start out to do this, almost 40% of the patients in SUPPORT were black.

Way beyond proportion of blacks in the United States obviously.

What does that mean?

One thing to me.

Even though saving lives and saving premature babies is an absolute wonderful goal and supported by everyone, we're not going to solve the problem of prematurity in the neonatal intensive care unit.

We'll solve it by prevention.

Solve by lessening the number of people born premature. By interventions we all know about.

The affordable care act, interventions on taking care of people, better education, better nutrition, et cetera.

So I want to make five points today less than a minute each but I think those are points we can agree on.

One, there is a difference between research and treatment.

Two, informed consent is required for both.

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Three, there's nothing special about standard of care research, that's said many times will be said many times again but it's true.

Four, randomization always deprives research subjects of the judgment of their physician and potential research subjects must know this.

Five, as Lois said, all these issues are governed by law.

We can't ignore that.

First that's a fundamental difference between research and treatment.

Differences that explain why we have prior IRB review system.

To put it briefly, treatment involves decisions made in a doctor/patient relationship where the physician has a fiduciary duty to act consistent with the best interest of patients.

With the patient's consent.

Research done by physicians has a purpose of generating knowledge for the benefit of other people.

Knowledge made generalizable by following a protocol.

A physician action must be guided by a fiduciary obligation to the patient.

Researcher has no such obligations.

That's relatively straight forward.

Second, although there's a difference between research and treatment, the document of informed consent applies to both.

This idea is if you're doing standard of care, doing treatment, you don't need informed consent, I have no idea where that came from.

In each case physicians and physician researchers have a legal and ethical obligation to obtain the patient's voluntary informed consent to any intervention that involves risk.

What those risks are, we can debate, we have started debating that already today and that's a lot of what IRBs talk about.

At a minimum the document of informed consent requires disclosure of material risk and as California supreme court said well, a material risk is any risk that might persuade patient or research subject not to accept the recommended treatment.

So risks of death for example, always have to be disclosed.

Third, there's nothing special or privileged about medical standard of care or so called standard of care research.

Standard of care, you should know this by now, is simply a term used to describe what doctors tend to do in various circumstances.

It actually has most application medical malpractice cases where show the doctor had a duty to follow standard of care and didn't do that.

It's a description of what doctors do, it's not technical or scientific or even a medical concept.

Standards of care come from a variety of sources, there's no entity that creates a standard of care, it could be from expert consensus panels, it can also be randomized clinical trials but also physicians at conferences, drug companies, habits in residency.

And most horribly I think they can come from doctors practicing defensive medicine because they worry about being sued so they do tests, which changes the standard of care.

Bottom line, there's nothing new or magic about standard of care that creates any difference in the type of consent you have to get.

Fourth when randomization is used to assign a subject to one or more arms of the study the potential risks and benefits of both arms when there are two for example must be explained.

Whether or not each could qualify under some circumstance as consistent with standard of care, this should be again relatively straight forward informed consent.

IRBs shouldn't be allowed to waive informed consent for research involving randomization.

Fifth, finally, there is law on this, there actually is a specific case that I urge everybody interested in this subject to read.

A Daniel Burton case it was decided in New York in 1982, it involved an experiment done in 1953.

A very similar to SUPPORT.

In a neonatal intensive care unit in New York City.

In which a patient Daniel was born prematurely was randomized and enrolled in a clinical trial shortly after his birth with -- it was assigned to high oxygen level without his parent's consent or knowledge.

The jury found in favor of Daniel, it should have been informed. Daniel went blind because he was in a high oxygen level, his -- and the court said two things.

An order to obtain informed consent for randomization was not excused because Daniel's treatment arm was in accordance with applicable 1953 community standards.

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And court went further to say if Daniel treatment was quote accepted medical practice, using it without informed consent deprive Daniel of having a physician using best judgment on whatever superior knowledge and skill and intelligence he has.

MODERATOR:

Your seven minutes are up.

GEORGE ANNAS:

One sentence.

So whether called standard of care research clinical effectiveness research patient centered outcomes research or research in context of learning healthcare institution IRB must review each study based on specific goals outcomes risks and benefits from the perspective of protecting the research subjects.

MODERATOR:

Thank you.

NIH.

KATHY HUDSON:

So in the Burton case which some of us did read -- thank you for citing that in your remarks, there was no consent whatsoever.

So what was that issue with -- there was no consent, not the specifics of what was included this that consent, is that correct?

GEORGE ANNAS:

No consent at all, it was just assigned randomly.

KATHY HUDSON:

It was remarkable in many ways because 1953 was well in advance of many of the norms we now adhere to.

So when you talk the community standard, what was it that the appellate court referred to when talking about that in the research context?

GEORGE ANNAS:

The appellate court referred to a physician making his best judgment.

In this case the physician was actually a resident and neonatologist resident who had -- was changing babies oxygen level based on what he saw the baby doing.

The most horrible part of that case actually had to do with the ophthalmologist who was examining the baby every seven days during this study and documented his eye site getting worse and worse and worse.

No physician could do that.

Only physician saw himself as pure researcher could document someone going blind and not doing anything about it.

KATHY HUDSON:

Researchers wouldn't be able to do that.

GEORGE ANNAS:

I hope not.

You're absolutely right.

At some point, researchers know they have to break the mold and help the subject.

MODERATOR:

Thank you.

OHRP.

JERRY MENIKOFF:

Thank you, professor for the helpful comments.

If I can pick up on the issue actually Dr. Hudson was raising, we also appreciate that you brought up the Burton case, we almost ended up mentioning it in our initial letters on this point.

Granted there wasn't any consent required back then but clearly this Court seems to be recognizing there's a difference between your doctor making a judgment even in the face of uncertainty versus being randomized in a research study.

So presumably had this been rectified in that scenario or some scenario now, what do you think if a court was looking at, presumably what would have mattered would be giving the parents enough information so they actually know what the physicians were worried about in terms of figuring out high oxygen or low oxygen.

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Which presumably would have been included -- what the concerns were on either end referring to SUPPORT case right now.

Does that make sense?

GEORGE ANNAS:

That's right.

They would do as all courts do, does the patient understand what you're asking them to do.

And what the risks and benefits are and alternatives are.

That's actually straight forward.

It doesn't require a 60 page single space consent form.

MODERATOR:

FDA.

ROBERT TEMPLE:

Two questions, one relates to the last one.

You see in your written comments in the Maklin et al. comments so on a major concern about not having the doctor make the doctor's best shot but where nobody knows what to do.

Is that a big deal?

I'm not sure the doctor is capable of -- you do definitely have -- I don't doubt you have to tell people the doctor is not choosing that you're randomized you do have to do that.

How worried are we about the loss of the physician's individual decision when nobody really knows what the right answer is.

That's -- o it's in the OHRP second letter, it's very prominent.

In these areas of uncertainty that seems odd to me.

GEORGE ANNAS:

We're really worried about it.

During the Clinton era his healthcare plan went down because people worried they wouldn't get their own physician, they wouldn't be able to choose their own physician.

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Under affordable care act the patient centered research is called patient centered research for a reason.

We're trying to focus on the patient.

And again, may not be -- I don't want to speak for the government.

Certainly a view of Americans that their doctor matters.

Who their doctor is matters, their doctor's judgment matters.

I don't think it's useful, if scientists think doctors don't know anything, they'll just make guesses, I heard hundreds of guesses a day.

We have trained them, we think medical education means something.

We put them through residency and fellowships.

We want their judgment over our own.

We value that very highly.

I would not want -- I think that would be the worst possible outcome of this discussion.

What we have to do is teach Americans their doctors that don't know anything and that they're better off flipping coins every time something has to happen.

I think that -- first I don't believe that's true.

But secondly, I think that would be very dangerous message to --

ROBERT TEMPLE:

Slightly more inclined to believe it's true at least sometimes.

Let me ask one thing that was in your written remarks.

It is of interest to me, I'll explain why.

IRB should never allow to waive informed research involving randomization of individual subjects standard of care interventions.

Does that imply you think if you were doing cluster randomization you might be able to not get consent?

We're interested in that.

We're all thinking about cluster randomization.

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GEORGE ANNAS:

That's a much more -- it is possible.

If you want to look at it, IRBs have to look at that individually, you could make an argument for some cluster randomization.

MODERATOR:

Thank you.

Can we get our panelists back on the stage, please.

PRESENTER CHARLES NATANSON

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MODERATOR:

Charles Natanson.

CHARLES NATANSON:

Good morning.

My talk today is on therapeutic misalignment and randomization to the extremes of usual care.

It has serious implications.

It can make you come to the wrong conclusion and hurt patients.

Two points to make today are critically ill patients receiving a therapy titrated to individual need, randomization to dosage extremes, has foreseeable risks.

Second, such trial designs in the absence of usual care arm may harm patients and have a limited ability to inform practice.

Trials that are high risk for therapeutic misalignment, trials of life-sustaining therapies, routinely adjusted for severity of disease.

You're testing two extremes of such a therapy.

Therapy is changed independent of need and there is no usual care control.

The SUPPORT study has the same properties.

Abbreviated methods and hypothesis, lower target range of oxygen saturation, 85 to 89% compared to higher 91 to 95 reduce severe retinopathy of prematurity or death of infants 24 to 27 weeks.

In order to blind caregivers to group assignments they use offset pulse oximeters to titrate oxygen therapy in infants.

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This was a displayed range that was presumably the routine target range of O2 saturation used in preterm infants.

What was actually the patient had in the low arm was oxygen saturation of 85 and in the high arm of 91.

As you move up here up until 92%, it was either 89 or 95%.

These are the outcomes of the study.

Shown on the left are end point on the right are P values, and middle and lower and higher saturation arm the O2 sats.

Because the practice misalignments created with randomization and the known risks of retinopathy, higher oxygen levels, and death, lower oxygen levels, these results are not unexpected.

Pre-term babies that were randomized to oxygen levels at the extreme high end of usual care developed more severe retinopathy.

Pre-term babies randomized to oxygen levels at the extreme low end of usual care, died more often.

There were two additional trials, that used the same design and methodology of the higher and lower oxygen saturation ranges and offset monitors.

They were started a year later and finished a year after--BOOST and COT--done in the United Kingdom, Australia and Canada.

Midway through those studies--the BOOST and COT--pulse oximeters were recalibrated.

They were recalibrated to lower oxygen saturations in the higher ranges and I'll show you that data.

This resulted in an unintended experiment in the pre-term infants.

It is potentially informative to the misalignment problem.

This shows the overall survival rates in all the patients in the United Kingdom, Australia and Canada before the pulse oximeters were recalibrated.

And in each one of those studies the odds ratio 95% confidence interval crosses the white line, the results are very similar and below on the bottom of that slide I show you the summary.

Prior to recalibration there was no significant difference in survival rates comparing the low and high oxygen target ranges across these studies.

After recalibration there was a shift very similar in all three countries.

And now there's a highly significant result.

After recalibration there was a significant difference in survival rates favoring the high target oxygen range across these studies.

What I hold, if practice misalignments are impacting outcome, recalibrating the pulse oximeters it should have the following effects.

In the low oxygen arm lowering oxygen saturation should worsen, creating misalignments, while raising oxygen saturation should improve outcome.

In the high oxygen arm, raising oxygen saturation should worsen making the misalignment worse.

Whereas lowering oxygen saturation should improve outcome.

This shows the O2 saturations in blue over time in the high target group and in the low group, and you can see in the right at the high oxygen saturation line the blue line is above the yellow showing that in the high arm they reached higher oxygen saturations.

And in the low ranges the yellow line is above the blue showing at the low saturation, the low treatment arm had more patients.

And thus there was a shift.

What happened with recalibration?

I realize this is difficult to follow but I'm showing you what happened in the highest saturations, 91 to 95% with the amount of time that was spent in the higher saturations.

Almost all of those arrows go down in the low saturation group, in the high saturation group in the United Kingdom and Australia showing that there was a decrease in time spent at the high saturations.

In the next slide I am showing you now in the mid to low ranges, there were increases, that is after recalibration the United Kingdom, Australia and high saturation arm there was an increase in time spent at the low saturation.

So what was the result of recalibration?

Decreasing exposure -- recalibration reduced oxygen exposure in both the high and low O2 saturation arms. That was the effect of recalibration.

In the high treatment arm, similarly in the United Kingdom Australia and Canada there was an improvement in survival lowering oxygen. It shifted to the right.

And if you look there at the summary statistic, decreasing oxygen exposure, that is getting less misaligned improved survival rates in pre-term babies already receiving higher than usual levels of oxygen.

And in the other arm, the low saturation arm, decreasing oxygen exposure, you see they are all shifted to the left.

Decreasing oxygen exposure worsens survival because they were more misaligned in neonates already receiving levels lower than usual care.

These effects of lowering oxygen exposure on survival were significantly and opposite comparing the low and the high oxygen target ranges.

The further you misalign the worse they got the more you return to usual care, the better things got.

So in conclusion, randomizing the critically ill to extremes of titrated therapies, creates practice misalignments which carry risks and do not represent usual care.

MODERATOR:

Your seven minutes are up.

CHARLES NATANSON:

Usual care control arm is essential to adequately monitor safety and inform practice.

Thank you.

MODERATOR: Thank you.

Now to the panel.

OHRP.

JERRY MENIKOFF:

Dr. Natanson, thank you for your work on this and a lot of your other work in this area.

So I'm curious if we can tease out in this scenario seems you're saying by the very nature of being at the high end or low end there are some generic risks to these infants that should have been disclosed and I'm trying to understand, is that different from other scenarios which my understanding of some of your similar work is that physicians are using their judgment in terms of where in these ranges patients are put.

I'm sort of curious if you could tease that out a little bit.

Is there a difference between those scenarios in which you're saying physicians are making judgments?

Are you indicating that's in fact what was probably happening in this scenario and therefore people were being assigned to one end or the other perhaps differently than the physicians might have judged had they not been in the trial.

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If that makes sense.

CHARLES NATANSON:

Physicians are titrating oxygen therapy.

The are titrating oxygen therapy based on many factors to an O2 saturation.

JERRY MENIKOFF:

So they are doing that as part of general and medical care, yes?

CHARLES NATANSON:

When you lower and split the O2 saturations to the extremes of usual care you change the titration, put people at extreme of usual care when a physician wouldn't normally do that.

And it was done independent of need.

JERRY MENIKOFF:

Thank you.

MODERATOR:

FDA.

ROBERT TEMPLE:

So when you say usual care control arm is essential, do you really mean a sort of middle arm?

CHARLES NATANSON:

No.

This is titrated therapy.

And you have to, as best you can, to determine many of the people will be in that range but no, there are people that are, as they have said, some of standard of care is down here, some of standard care is down here and some is in the middle.

You have to create a control which is titrated care.

What physicians normally do based on many factors.

There's two risks here.

Two competing risks.

There's risk of death and risk of blindness and physicians based on individual patients and what the risk benefit of multiple comorbidities are made come to a decision about how to do that titration.

ROBERT TEMPLE:

So but are they titrating to a particular oxygen saturation?

CHARLES NATANSON:

They are titrating to many different factors but oxygen saturation is one of them.

You'll find a saturation for a particular child that has minimal risks. I mean I guess I would say to you the way I would describe it to you is that if an infant was at a 30% oxygen, okay, they would consider that still risky but minimal risk.

And had a sat of 92, they would probably leave them alone.

And in this study what you would have done is you would have for no particular reason in order to get them into the trial lowered them down to 89% which put them at increased risk or you would have increased them up to 95% which increases risk of retinopathy for no particular reason.

ROBERT TEMPLE:

So when you say usual care you would have meant let doctors use their judgment taking all manner of things into account as opposed to trying to get to 85 to 89 versus --

CHARLES NATANSON:

It's more than judgment.

They also use many physiologic end points

ROBERT TEMPLE:

Okay.

CHARLES NATANSON:

And they use based on studies that have been historical studies, in their clinical experience and joint experience, there's a lot of data that goes into usual care.

It's not willy nilly random.

They train neonatologists for three years, and within that three years of training they learn how to manage patients, using these various risk benefits.

ROBERT TEMPLE:

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Another criticism that's been offered of this though is that it took, in order to try to show a difference, took relatively extreme versions of usual care.

Very low and very -- really, really high.

So what do you think about another possibility of having a three arm with one in the middle, one high and one low?

CHARLES NATANSON:

It doesn't seem like you have a hypothesis.

If what you're doing here is a physiology study, lowering and raising and you have no way of determining what usual care was -- the risk you have here, think about it, in the study that was done with COT and BOOST before recalibration.

When after recalibration you found this big effect between the two.

It sounds most likely that both of those arms were harmful, that's why you saw no effect and you had no way of knowing.

You had no controls, no usual care, and this was a rapidly lethal disease with a high mortality rate.

And there is no signal and you're shooting blind.

I think it's high risk and in the end you have no controls to make firm conclusions.

So instead of spending your time going to the extremes of care, why don't you spend your time defining usual care, getting a usual care control arm and then have a hypothesis, not raising or lowering.

Hypothesis being, is lowering better?

Should we lower and compare it to usual care.

Or is raising better and let's compare it to usual care.

I don't know what you learn comparing lowering to raising.

It's a physiology question that doesn't give you inferences and you'll come to the wrong conclusion.

MODERATOR:

NIH.

KATHY HUDSON:

No questions.

Thank you.

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MODERATOR:

Okay.

Thank you.

So I had warned you I would take the moderator's prerogative and find a natural break, I'm grateful the presenters and to the panel for really keeping us on time.

I haven't had to be a despite about it so thank you all.

So in that regard, seven minutes exactly seven minutes for a break.

Okay?

From we will start promptly with our next speaker at 10:33.

I will say to those in webcast land we know there was a technical issue with our audio on the live stream.

That issue has been fixed, and we will have all presenters available for on demand viewing as soon as possible after today's hearing.

So we do apologize.

Thank you.

Exactly 6 and a half minutes now.

Terrific. Our next speaker is Vera Sharav, I apologize, I had not realized we had slides that I was actually supposed to be advancing.

I was conscious of the clicker so thank you.

PRESENTER: VERA SHARAV

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VERA SHARAV:

Thank you for giving me the opportunity to speak.

You have my testimony, this is a concise kind of.....

I'm going to repeat several things that have been said before because I think they're repetition.

Of course the first is that research is not standard of care.

The difference should not be blurred.

In standard care, as we have heard, a doctor's fiduciary responsibility is to prescribe treatments that serve each patient's best interest adjusted in response to each patient's individual fluctuating need.

Research treatment is predetermined by a protocol that seeks to resolve uncertainty and contribute generalizable knowledge.

Ethical research requires voluntary informed consent, that's the cornerstone.

Every patient who is asked to volunteer for research should be informed honestly about potential risk of foregoing individualized care.

Inherent risks in treatments used in standard care may be magnified within the constraints of research.

For patients with complex illnesses, unstable clinical needs particularly in critical condition, even a life-saving treatment at an inadequate or excessive dose can be lethal for some patients.

The catalyst for this meeting is the debate ignited by the SUPPORT study entailing two randomized experiments conducted simultaneously on premature vulnerable babies.

None of the babies in SUPPORT received individualized adjusted oxygen supplements, as they would have in standard care as you have seen the examples.

Death was a primary outcome measure in each of the experiments.

The oxygen experiment compared restricted low versus high oxygen intake and the outcome measure was death or retinopathy of prematurity.

Ventilation experiment as well compared continuous positive airway pressure to usual care outcome measure was death or lung disease.

Yes not a single IRB approved consent form mentioned death.

SUPPORT defenders deny the death was even foreseeable a risk.

Well then why was death the primary outcome measure?

Death was identified in the protocol as well as in the published report, but not consent documents.

Evidence from multiple studies spanning 50 years confirmed risk of death when premature babies' oxygen intake was restricted.

The risk was therefore foreseeable and should have been disclosed.

If the intent of SUPPORT was to find a safe oxygen level to improve premature babies' survival without retinopathy prematurity, protocol deficiencies undermine that goal as we have just seen in the presentation before me.

Lack of a current practice control group impeded both safety monitoring and also obtaining generalizable knowledge.

Randomization to restricted oxygen intake disregarded babies' unstable clinical condition or oxygen need.

The SUPPORT criteria for intubation extubation as you saw in the slide from Dr. Carome, researchers acknowledged they were more severe than have been used in any trial and more severe than used in most network centers. CPAP babies were subjected to multiples of these painful procedures. Parents were deceived. Consent documents indicated because all treatments proposed a standard of care, there is no predictable increased risk for babies.

The death toll of SUPPORT, 130 babies randomized to the low oxygen group died and 107 randomized to high oxygen group.

How many deaths and how many brain injuries can be attributed to SUPPORT?

Tuskegee was conducted before federal regulations established parameters of ethical and legally permissible research.

Before an authorized agency existed.

Before mandatory IRB review.

Federal regulations were enacted after Tuskegee to prevent future unethical research.

SUPPORT was grossly unethical by U.S. and international standards.

Parents were deceived about foreseeable risks, death was concealed, babies' safety was sacrificed to protocol dictated procedures that deviated from standard care.

Defenders of SUPPORT view informed consent as an obstacle that slows or impedes certain research projects.

They complain that obtaining informed consent requires time and effort.

SUPPORT encountered strong resistance from the mothers.

47% revised to give their consent, their permission really, for their babies to be enrolled.

The frequency of approaches to obtain consent were one in 11.

How many approaches before we say it's coercion?

How many times must a mother say no before her refusal to consent is respected?

Research extremists led by NIH directors attempt to legitimize SUPPORT, arguing it is in the category of comparative effectiveness research.

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MODERATOR:

Your 7 minutes are up.

VERA SHARAV:

Which they insist pose no greater risk.

Their claim is contradicted by multiple protocols dictated deviations from standard consent.

From standard treatment rather.

They seek a waiver from federal informed consent disclosure requirements for this comparative research to facilitate medical experiments without disclosing risk, without prior parental permission or knowledge.

MODERATOR:

Please wrap up.

VERA SHARAV:

Against their will. I will right now.

If SUPPORT serves as prototype for future comparative effectiveness research it foreshadows how the rights and safety of patients in such experiments are likely to be violated.

MODERATOR:

Please stop.

SHARAV:

We must preserve and uphold protections that separate civilized medicine from pre-Nuremberg experimentation, thank you.

MODERATOR:

Thank you. NIH.

KATHY HUDSON:

I would like to make the point the death rate of babies within the study was actually lower than the death rate of the babies who did not enroll or were not enrolled in the study.

There are a number of factual misrepresentations but I won't correct those.

I want to ask about the comment about the rate of individuals failing to agree to participate.

It's not my view there's a particular wholesome level of participation and these parents are in a particularly vulnerable time where they had just given birth to extremely high risk infant and they're being asked to participate.

It's another piece of information.

Another thing that's put before them.

I'm not particularly concerned about individuals saying no.

In fact, that's the basis of why we have voluntary consent is that people always have the ability to say no, thank you.

VERA SHAVRAV:

I'm quoting from articles by SUPPORT researchers who complained and made a cost benefit analysis of what it costs to get a consent and in that journal article in Pediatrics, they argue that it costs too much, it took so many refusals and times they had to approach, this is coming from researchers, not me, that they are asking that permission be given after the babies get enrolled in such a trial.

Get it? Informed consent after.

And they even say at that point the parent can decide whether information obtained in the trial -- the consent they get would let them choose whether to allow information obtained in the trial to be published.

MODERATOR:

FDA.

ROBERT TEMPLE:

Just one question.

Most of the critics including OHRP, Dr. Annas and others, have said they thought the trial was a good thing to do but they were concerned about the consent and those things.

You seemed to be saying you thought the whole trial was a bad idea.

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Do you want to elaborate?

VERA SHARAV:

I do.

In a sense I think SUPPORT provides us with a window into how extreme researchers can go if not held back. That really what we need is more stringent regulations or enforcement.

Right now there's no enforcement.

This kind of a trial is so complicated. So many things were happening to these very, very critically ill vulnerable babies.

Everything is randomized, nothing about their struggle to live, to breathe, was taken into consideration at all.

It was all kind of nullified as if they were animals.

This is not fit for humans.

I absolutely don't think this trial was properly done.

ROBERT TEMPLE:

That must be --

VERA SHARAV:

Remember, I am not a scientist.

Go to the public and see whether, if they would have disclosed even 50% of what they should under federal REGS they would have gotten even less mothers, if any.

What responsible mother would put her baby into a trial where death is at every corner in addition to the threat that the baby has in the first place?

MODERATOR:

OHRP.

JERRY MENIKOFF:

Thank you for the comments.

No question.

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MODERATOR:

Thank you.

MODERATOR: Lisa Hurley.

Is it Lisa, Elisa Hurley?

I remember those early days when the lab technology came along and there was debate how to pronounce it.

PRESENTER: ELISA HURLEY

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ELISA HURLEY:

Good morning.

I am here representing PRIM&R, Public Responsibility in Medicine and Research, and just to let you know the comments that I'm going to summarize are a product of a standard public policy process which involves our public policy committee and staff (that would be me) drafting comments, comments are then approved by executive committee on behalf of the Board of Directors and then submitted as PRIM&R's view.

In our comments what we do is we propose a framework to guide IRBs when they're asked to involve research of random assignment of patient subjects to interventions which fall within the standard of care provided to patients outside a trial. Before I go into detail about that framework I wanted to highlight two overarching principles that shape and guide PRIMR's comments.

First, PRIM&R believes protecting the rights and welfare of human subjects should never be compromised in the service of the desire to expedite research, regardless of how valuable that research might be; and that a primary if not the primary mechanism through which protection is operationalized is the informed consent process.

Second, PRIM&R recognizes that practicing medicine on a strong evidence base is essential if scarce resources are to be used in the most patient centered and ethically sound way; seeking to fill gaps in knowledge about the relative merits of different accepted interventions is crucial if we want to add to that evidence base.

However, research to improve our understanding of the correct standard of care, sometimes called comparative effectiveness research, is not unique from the perspective of research protections. As with any human subjects research, those seeking to enroll patients to compare standard of care interventions must explicitly tell them that they've been asked to participate in research and what this means for them.

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So now to our framework.

So we outline six questions we recommend IRBs ask concerning protocols and informed consent processes in trials that involve random assignment interventions, all of which are within the standard of care; so I'll quickly run through that list then I'll focus more on three questions that are at the core of our view.

So here are the six questions:

First, have the investigators established that the medical interventions being compared are within the accepted standard of care and that doubt exists regarding their relative effectiveness.

Second, how will potential subjects be informed about the nature and potential harms, burdens and benefits of the interventions being compared.

Third, how will potential subjects be informed that they are being asked to participate in a study comparing two interventions and that if they don't wish to participate, they will instead receive standard of care.

Four, how will potential subjects be informed of any available alternatives to the interventions being offered in the study.

Five, what burdens and potential harms -- beyond those inherent in the interventions being compared-- are added by participation in the study.

And six, how will potential subjects be informed of any of those additional risks?

So a little more detail about questions in 2, 3 and 5 of that framework.

Question 2, how will potential subjects be informed about the nature and potential harms, burdens and benefit of medical interventions being compared? So we argue that in a research study involving the comparison of one or more standard interventions, the IRB should be satisfied that someone will have engaged potential subjects in the process of discussing the nature of potential benefits, harms and burdens of the interventions compared; and investigators have a responsibility to explain how that process will be carried out.

But we acknowledge in our comments that guidance rather than regulation is needed here because this process of disclosure and discussion of who does it, when it takes place and what exact form it takes, can and should vary from setting to setting and from intervention to intervention.

How will potential subjects be informed that they're being asked to be part of study comparing medical interventions and that if they don't wish to participate or continue in the study they'll receive standard care?

We argue that as in other research, it is essential that patients asked to enroll in a study comparing two or more standard interventions be in a position to make an informed decision about participating and what is entailed in entering the study.

Thus the IRB should ensure there is a plan or process in place for informing subjects first that they're being asked to participate in research.

But potential subjects must be made aware of what it means to become a research subject in this particular context.

For research that involves randomizing subjects between standard of care interventions, the basic choice for potential subjects is whether they wish to have the intervention that their physician recommends based upon her best, albeit not fully supported clinical judgment, or have it chosen by a process governed by rules that are laid out in a study protocol.

The key for us in the IRB should be to ensure that the investigator has set forth how subjects come to understand that they have this choice as regards the specific intervention being studied, between remaining in a therapeutic doctor-patient relationship and entering an investigator-subject relationship, in which case their physician won't routinely be making personalized clinical decisions about the use of interventions in their study.

The fifth question of our framework that I wanted to go into more is: what burdens and potential harms beyond those of the two or more interventions being compared, are added by participating in the study?

Deciding when a study involves harms beyond those inherent in each intervention, when provided as standard care, requires nuanced assessment. The specific potential harm added by research participation will necessarily be case dependent.

So we don't think research always adds harm.

The IRB must determine whether investigators have thoroughly examined and identified the burdens and potential harm to potential subjects that are added by participation in this study, over and above the risks of receiving either intervention being compared, and that they have developed an adequate description of added risks for the informed consent process.

We urge OHRP in our comments to provide guidance to IRBs on how to identify and evaluate these additional burdens and risks.

In our comments we provide examples. In the interest of time I'll only mention two.

For instance some burdens and harms may arise in research because subjects in the study may undergo additional testing and monitoring, from blood draws to imaging, that may create new burdens which patients receiving the intervention as ordinary care wouldn't be exposed.

Or another example we give is as a result of procedures that mask certain data sources, such as blinding, a physician investigator may not receive information she would have received when providing ordinary treatment giving rise to additional risk. We go to say any such additional risk of burden identified must be clearly explained to potential subjects in the informed consent process or form.

So to conclude, we acknowledge it's complicated for IRB investigators to apply the Common Rule and general ethical guidelines about informed consent when research involves standard of care interventions, given the added complexity like separating like potential harm of existing interventions from those added by enrolling in the study, and adequately explaining to the potential subjects differences between receiving interventions as a physician's patient and receiving possibly that same intervention as a subject of a trial.

MODERATOR:

Your seven minutes are up.

ELISA HURLEY:

However we again emphasize that from the perspective of research protections, research to improve our understanding of the correct standard of care is not special. Thank you.

MODERATOR:

Thank you. Turning to the panel. OHRP?

JERRY MENIKOFF:

Thank you. Very helpful.

I want to address one point you made in your written comments, so this is from page two.

"Furthermore we assume that what is being studied involves something about which patients usually choose among alternatives, that is, the sort of changes in routine care that are first discussed with patients."

You note, you footnote distinguishing it from institution wide administrative procedures, et cetera.

What about, and the facts of SUPPORT are a good example, others in their comments will raise the issue, will discuss- well, doctors in general didn't discuss the level of oxygen with the patients even though they're looking at various criteria to titrate this to particular patients.

Was your intent in this comment to say that the fact that doctors don't usually discuss this aspect of care with patients means you could for example in the study randomize to different values and therefore not have to disclose this to subjects?

ELISA HURLEY:

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No.

So there was some discussion amongst members of the committee that came up with these comments about this question.

We decided not to take a stand on the issue, though there are those that have the view that that discussion should be happening, if it isn't that's a descriptive matter but normatively it ought to be happening in the case, in the clinical care case. So I think that it is a little misleading that we have that sentence in there, because it's not the case that we want to limit it to cases where what's happening actually is that, that discussion is happening in the case of just regular care.

JERRY MENIKOFF:

That's a helpful clarification.

Thank you.

MODERATOR:

NIH?

KATHY HUDSON:

Thank you very much for a useful framework and for presenting today.

You make an interesting -- you make an interesting point in your first comment about establishing that the medical interventions are within accepted standard of care, there was clearly commentary this morning about whether or not the standard of care is an appropriate or useful term. So I would be interested in your perspectives on that.

And in addition, you raise the suggestion that an IRB may need to consult with relevant experts in order to really ascertain and verify the investigators' determination of whether this is really is within the standard of care, is in fact the case.

So I would be interested in your comments about whether that is a routine or unusual occurrence to call in extra experts for IRB?

ELISA HURLEY:

Right.

I would think that would be, to your last question first, that that would be unusual but the idea would be if the IRB feels that's needed to establish that, that would be an option that would be encouraged, if say if guidance were to follow this -- this framework.

So regarding the standard of care, we included in our comments a footnote about this controversy, about that particular phrase and whether -- we chose to use it because it was used in the Federal Register notice. And so I'm not sure I understand what exactly you wanted to know about that.

KATHY HUDSON:

I was asking whether or not you felt like there was enough of a certainty around what is the standard of care to be able to usefully employ that in this kind of framework.

ELISA HURLEY:

I think, what I think would be helpful, again if we were to follow this guide that PRIM&R put out forward guidance would be some sort of definition of what qualifies as standard of care.

What sort of practice within the community, what kind of literature supporting that would make something qualify itself as standard of care.

MODERATOR:

FDA.

ROBERT TEMPLE:

Thank you, but no questions.

ELISA HURLEY:

Terrific.

Thank you.

MODERATOR: John Lantos.

My job is getting easier.

PRESENTER: JOHN LANTOS

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JOHN LANTOS:

Thank you very much for holding these hearings.

I speak today as a grandfather.

Seven years ago my wife and I were blessed with twin grandchildren, Will and Sam.

They were born at 23 weeks at a hospital that was participating in the SUPPORT study.

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Too premature to be eligible.

Sam died at 30 hours of age from respiratory failure and Will spent four months in the NICU and survived with severe retinopathy.

After laser eye surgery, he has no peripheral vision and his central vision is 2200 with glasses.

But he is doing well, full of curiosity, laughter and love.

We didn't know about the SUPPORT study.

I wonder how our family would feel if the twins had enrolled.

Imagine if they had.

If Sam then died as he died and Will developed retinopathy as they did, we would have blamed outcomes on the study and second guessed the decision to enroll them.

We would wonder whether they would have done better if doctors used their clinical judgment rather than a research protocol.

If we later read that the consent forms were inadequate we would have been outraged, we would have felt like we had been deceived and our grandchildren harmed as a result.

Hell, we probably would have sent money to Sidney Wolfe instead of the March of Dimes.

Imagine another scenario.

Imagine they had been eligible for the study, and their parents read consent forms that explained death lurked at every corner and the research risks involved death, eye disease and neurologic damage; imagine after reading these risks they decided not to enroll their babies in the study.

Sam then died as he died and Will developed eye disease as he did.

In that situation we probably would not have been outraged.

But we should have been.

In that situation, sadly, no Federal agency would have scrutinized the consent process.

No advocacy groups would have called for public apologies or criticized the cocky use of idiosyncratic clinical judgment, but they should have.

After all, babies in the study were at higher survival rates and were less likely to develop eye disease than babies not in the study.

Babies whose treatment followed precise protocols did better than those offered individualized treatments.

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Consent forms should explain those real and likely possibilities and if they do not, they are not empowering people to make informed choices, they are scaring them into making uninformed ones.

In comparative effectiveness research studies, OHRP should insist that potential study subjects be given accurate information about the risks and benefits of both research and non-validated therapy.

That is the only way to ensure choices are true informed.

When consent forms overstate risks of research, make no mention of the risk of conventional therapy, don't say research subjects might be better off than patients who are not in studies, they are misleading and dangerous.

Misleading inaccuracies push patients away from safe, well designed studies and towards treatments with unknown and often greater risks and babies die as a result.

I say babies die and I mean that literally.

As you go about your deliberations here, please don't think this is a game in which whoever puts the biggest possible list of possible risks on the consent form wins; most consent forms do that quite well.

Instead the winners should be the one who puts those risks in context to help understand that by consenting to research, they may be avoiding some risks and exposing themselves to others.

You have a huge, difficult responsibility here in developing guidelines, getting it wrong in either direction could lead to avoidable deaths.

Informed consent is the ethical cornerstone of both research and clinical practice.

On this admirers and critics of the SUPPORT study agree.

We disagree where the greatest dangers lie.

In comparative effectiveness research, or as Alice Dreger put it, studies on commonly used therapies, where none of the therapies is experimental, research studies are as likely to reduce risk as they are to increase it.

Why?

All the risks of a well designed comparative effectiveness study are inevitably present for patient whose are not in the study.

If that was not so, if we knew which one was safer or better we should not approve the study.

In such situations, consent, though very important, is not the crucial issue.

The crucial issue is whether there was true uncertainty.

Doctors and scientists who designed the SUPPORT study understood this, they did not think it was risky to be in the study, so they didn't put this in the consent form.

Doctors just hate to say that they don't know something.

I am a doctor, trust me on this.

When they do say it, we should take them at their word.

Like when a surgeon says they don't want to operate, listen to them.

How ironic then when all the expert neonatologists around the world acknowledge they didn't know which treatment was best for preemies, bureaucrats in Washington and New York insisted that those doctors did know or should have known; the sheer chutzpah here is mind boggling and it would be comic if the consequences were not so tragic.

Non-validated therapy is often more dangerous than careful research.

That statement- non-validated therapy is often more dangerous than careful research- should be part of every consent form for every IRB approved comparative effectiveness trial.

I hope that the federal regulations that come out of these hearings protect babies from the misleading information that comes from erroneous ideas of the risks of research and the safety of non-validated therapies.

Our children and our grandchildren deserve such protection.

Thanks.

Thank you.

MODERATOR:

We turn to the panel, FDA?

ROBERT TEMPLE:

I find most of what you said sympathetic.

But the main criticism actually in the study was not the study, or that treatments were unknown, it was there wasn't enough information given to the people entering it. Any comments on that part, particularly?

JOHN LANTOS:

I think figuring out what information to put on the consent form is tricky.

I agree with Sidney Wolfe, the New Zealand folks got it just about right.

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To me the more interesting thing about the experience in New Zealand was two things.

One, they got it right because they worked closely with parent advisory groups to develop the consent form, and I think it's a model that ought to be used as a template for what ought to be on consent forms, but the second interesting thing, they had more people consent in New Zealand than here, so the idea some speakers mentioned that if all risks are accurately described people would not consent, does not seem borne out by that experience.

MODERATOR:

NIH.

KATHY HUDSON:

No questions but thank you for your presentation, it was elegant and poignant, and also for the work you have done in the past. Thank you.

MOEDERATOR:

OHRP.

JERRY MENIKOFF:

Thank you, Dr. Lantos.

You've played a major role in this debate.

JOHN LANTOS:

You too, Jerry.

You too.

[LAUGHTER]

JERRY MENIKOFF:

Thank you for that.

It's interesting as I read more of your comments, it sort of gets back to Bob Temple's point, I'm not sure how far apart we are.

There are claims made by you and others about regulators looking for massive lists, et cetera, et cetera.

I actually learned about the New Zealand consent form when you published that, and you had the quote from it, and we have gone on record, the Federal government has gone on record, is all you needed in this consent form was a couple of sentences indicating, hey, there were risks, and what we're talking about in terms of those sentences, it's great to know you have more people consenting there, there are

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ways to write appropriate consent forms to do the right thing ethically, exactly your point about getting appropriate consent.

The notion certainly from OHRP's side, we have said from the beginning, in our first letter, this was a very important study to do; but all you needed to do was, and this gets back to your other point, and I'm asking about this, in your recent New England journal piece which is very helpful from last week for those who hadn't seen it, you are suggesting in these comments, if there's some uncertainty, then there's almost nothing to disclose to subjects.

But there's never 100% uncertainty and in this scenario different institutions were in fact making judgments and it wasn't just like throwing darts. Many institutions kept the infants for example in the middle of this range. And there was information out there that might say that's a reasonable thing to do

And so adding these two pieces together, I don't see that certainly from OHRP's viewpoint, we're very far apart.

All we were asking for, and we have gone on record about this, were a couple of sentences saying there were risks that the professional community were worried about on the low oxygen end, and if this study was in fact moving a lot of infants closer to that low oxygen end, in terms of very appropriate informed consent that you're concerned about, shouldn't you have in a few sentences in there letting the parents know about that.

And we're not talking a whole array of risk that you're inappropriately scaring people with, and again, it's great to hear that you have done that you would have been able to do the study; I was thinking what you were thinking, many people here or some are complaining you couldn't have done the study otherwise, you could have.

In fact they did a New Zealand and I wasn't aware they got a greater --

JOHN LANTOS:

So here is my question back to you.

I think there's some confusion about this from people I have talked to, and as head of OHRP maybe you can clear it up.

Is it permissible now to say in the consent form, for a study like SUPPORT, babies in the study might be better off than baby babies who are not?

JERRY MENIKOFF: I don't want to give a personal viewpoint as opposed to official regulatory position.

If you're going to put a statement like that in there, you should clarify exactly why you think that happens.

Maybe Dr. Hudson will say something about this, this is an ongoing debate about the general issue of -- are you talking an inclusion effect..? Why do you think they're better off? In terms of being better off,

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there has been a huge debate out there, and there's actually not all that much evidence, these are hard studies to do in terms of clear cut evidence.

JOHN LANTOS:

Could you say that you don't know that they'll be worse off?

JERRY MENIKOFF:

Again, I don't want to give an official position on that, but I don't think this --

JOHN LANTOS:

So this is where, in answer to your question, there are subtle differences that need to be clarified.

JERRY MENIKOFF:

This is something to be clarified amongst HHS in general and probably all the Federal Government, but let's be clear, I don't think that was the statement that was a big issue in terms of this study.

It was specific facts about being randomized to one or another arm, and what the profession was concerned about was the risks, and that those risks were not disclosed.

MODERATOR:

We will need far more than 12 minutes to resolve that.

But thank you.

MODERATOR:

Benjamin WILFOND.

PRESENTER: BENJAMIN WILFOND

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BENJAMIN WILFOND:

So thank you, Dr. Jones and the rest of the panel, to address you today.

I will begin -- I'm not going to be talking about SUPPORT today. I'll make a few introductory comments and then talk about another study, that happened 20 years ago, to frame my responses to three questions OHRP raised.

Speaking both from the vantage of an IRB member for over 20 years as well as a pediatric pulmonologist who spends Friday afternoons in the NICU, we're constantly trying to figure how to do things better.

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I think there's also a lesson that we in research ethics can learn from the phenomena of quality improvement in healthcare which is trying to look at ways to improve systems, and acknowledging that part of the challenge we face are areas that relate to systems failures and the best way to improve is by trying to improve the system rather than blame particular individuals when things go not as ideally as we might want them to go.

I think there's widespread agreement that our current approach to informed consent is flawed.

A number of speakers mention social science studies that show that even with good approaches to written documentation of consent, that people often misunderstand what is going on and many consent forms do not do an ideal job of explaining things.

So we need to figure out better ways of improving the informed consent process for informed research, and if informed consent is waived, think about better ways to engage the public.

A lot of our discussion today is really focus on distinctions between research and clinical care and distinction between randomization within research versus randomization within randomized clinical practices. I also think that concepts of foreseeable risk and waivers of informed consent, which are fundamental to the regulations, can be interpreted differently by people as we're trying to apply them.

You have my written comment, and my written comments describe in a little detail the Wisconsin newborn screening trial that was done 20 years ago. I want to bring this to everyone's attention, because this is an example of a study in which informed consent was waived, important information was learned, and in fact, individuals were probably harmed by their participation.

In this trial,-- results-- people in Wisconsin, their infants were randomized, to receiving results about cystic fibrosis screening either at six weeks of age or at four years.

All those identified with CF were then treated according to a standard protocol.

The study was reviewed by range of IRBs, NIH and community groups, and there was a decision that informed consent for the study could be waived, but there was also acknowledgment that it was very important to try to do our best job to let parents know about the study, if possible, and what was learned from the study was in fact that there were better outcomes from the detection of cystic fibrosis in terms of nutritional benefit, but in fact, in a number of cases individuals diagnosed earlier were harmed by earlier acquisition of pseudomonas.

Let me quickly come to the questions before the panel.

I think for the first question, I think the important thing is that efforts to improve care can be helpful or harmful regardless whether they're done within the context of clinical care or whether they're done within the context of research.

I also think risks need to be contextualized.

The contextual risk of clinical practice are fundamental to helping people understand what's going on and the risk of research themselves may not be that much more than the underlying risk of that clinical care.

It is important for parents to understand both the clinical aspects and the research aspects of that, and whether that occurs within a research informed consent form or part of the discussion, both are possible approaches to doing this.

Regarding the issue of randomization, it's not clear in all cases randomization is necessarily a risk.

We think about Wisconsin where all the infants were randomized, either we get results early or the results late.

At the same time in Colorado infants were screened, in Maryland no infants were screened, in Connecticut some were, some weren't. So it's not clear that infants in any one of these states were harmed differently than others, but it's only from Wisconsin that we learned over time how to do this better.

In summary, I think that the risks of standard treatments are not the risk of research and that research comparing standard treatments is the best way to identify risks of clinical interventions.

We need better approaches for informed consent to focus on helping prospective participants understand the crucial aspect of research; sometimes consent can be waived, but this does require active and innovative community engagement to reach those patients so they know about this.

I think there are next steps. I think we need ongoing discussion of these issues that are raised today.

I certainly notice a number of places where there was some agreement between people with different views about this.

We need a lot more empirical social science research about public attitude and novel approaches to formed consent.

Finally, we need to adopt a quality improvement model for thinking about these ethical issues and thinking about how we can improve things going forward.

Thank you.

MODERATOR:

Thank you. To the panel now, FDA.

ROBERT TEMPLE:

No comments.

MODERATOR:

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NIH.

KATHY HUDSON:

So you talk about CF screening that randomization, the randomization procedure was not a risk.

Can you talk -- and clearly there were different viewpoints about whether or not randomization within the SUPPORT study was or was not in and of itself a risk versus being randomized by the random provider that happens to be covered by your health plan or the hospital which happens to be in your neighborhood.

Can you talk a little bit more about when does randomization become in and of itself a risk versus when in your view it is not?

BENJAMIN WILFOND:

I'm not sure if randomization itself is a risk as much as it's what people are being randomized to.

So I think for example, in circumstances where we're comparing new drugs and placebos.

There's very different benefits and risks to those two things.

I think when we're talking about standard interventions that are standardly being used, I don't think there's a substantive difference between context which people are randomized to one or the other versus the circumstance where one hospital is only doing version A and one doing version B, and there's a third place when each does it differently.

I think all those are similar to each other. And are more similar than they're different.

MODERATOR:

OHRP.

JERRY MENIKOFF:

Thank you so much for your comments.

I'm reminded of discussion with Dr. Lantos because as some people here know and others don't, you played a major role in critiquing what OHRP did in this study. You're a leader in the bioethicist letter New England journal published saying these horrible things about OHRP. Overreaching, that conclusion of substantive merit.

So bear with me for a few moments, I love the example you give now here, the more I hear from the discussion with Dr. Lantos I don't see we're far apart.

There are a few sentences that should have been in the consent form and so let me explore -- so your scenario in cystic fibrosis study, which I don't deny is an important study, my understanding was the

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waiver of consent was with regard to you were doing the testing on all these blood spots and it was not at the time in fact even standard care to do that.

Right?

In terms of parents who didn't get the information for four more years, they weren't harmed beyond -- you weren't doing additional things giving additional information, they might not otherwise have gotten at that point.

That is a difference scenario, let me spell out, than issues in SUPPORT.

You then discuss in written comments about the unforeseen harms during the study, if I understand you, you're talking about the harms to the parents told immediately, that you unblinded results on half the infants who got the test done and had CF, and then applying proposed treatments to see if starting day one when you don't even know a baby has cystic fibrosis, see if this treatment we're in the sure whether it works.

You consented those parents.

Yes?

BENJAMIN WILFOND:

Correct.

JERRY MENIKOFF:

Your point trying to tie in SUPPORT was that some of them ended up having bad things happen to them.

You point out some got pseudomonas infections, and that was not an identified risk.

Nothing OHRP was trying to say in the SUPPORT study would have had any problem with any of that.

We were not trying to imply that when you're doing a study and measuring 100 things, not with pre-supposition that any particular one is a problem, but you want to look at a bunch of things to see whether or not you get a beneficial result, that you suddenly have to have pages and pages of results, you measure this, maybe there's an outcome relating to that.

The clear point is when the clinical community is out there, concerned that a particular treatment, a particular type of standard care or whatever, has a risk that everybody, that a lot of clinicians are worried about, and you as part of that study intentionally move the care of a particular infant or particular adult to that treatment, you should disclose that risk.

In your scenario here, it wasn't the case that when you were starting treatments, the clinicians, a good chunk of the clinical community, knew they were going to get pseudomonas infections, and we know that and it's admittedly disputed, but we're concerned about it but were not going to mention that in

the consent form, though we're asking the parents to agree to this treatment. That was not the scenario, right?

BENJAMIN WILFOND:

Correct.

I think the point of that scenario is to make the point about this -- the potential possibility of randomization not in and of itself causing risk.

I want to say in a quick response, I think you're correct we're not necessarily that far apart.

And like John, I would agree that the consent form New Zealand did a better job.

I think where we're far apart, I think that, moving forward, trying to figure how to do this better, it's not clear to me that the risks that occurred in SUPPORT were so great that what happened to that study failed the regulatory standards.

MODERATOR:

We have to wrap up.

BENJAMIN WILFOND:

Okay.

Thank you.

PRESENTER: ROBERT DANNER

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MODERATOR:

Robert Danner

ROBERT DANNER:

Randomization to the extreme of usual care range has very real risk.

And that needs to be understood by both IRBs investigators and disclosed to patients.

Before I start I need to disclose that I am on annual leave and speaking as a member of the public.

My comments are not intended to represent nor construed as views and policies of HHS or NIH and all the information that I'm about to present is public.

As Chuck Natanson mentioned, life-sustaining supportive care is often titrated based on multiple clinical factors.

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Doing this has variability to it.

It has variability both introduced by clinicians and by the patients, but it is not random.

Randomization to either end of routine care range changes care independent of clinical indications and the results of these trials are difficult to interpret in the absence of routine care arm.

To give an example of what can happen in a trial like this, I'm going back to a very old trial.

And this also demonstrates that this is not a new problem unique to SUPPORT.

This has actually been going on quite a while, particularly in critically ill patients.

This is a simple trial looking at acute respiratory distress syndrome.

It does a very, very simple thing; it alters the size of the breath given by a mechanical ventilator and randomizes patients to low or high breaths.

The 12 ml per kilo breath was considered or called traditional tidal volume.

A big question that I want you to think about as I present this data is that traditional tidal volume, really a control group, that is how it was used by data safety monitoring committee that looked at that time trial.

So before randomization tidal volume and severity of the disease were linked to each other.

And physicians were decreasing the tidal volume patients were getting when they had more severely injured stiff lungs that was leading to high pressures on the ventilator.

This is the distribution of tidal volumes prior to randomization.

As you can see, to go into the 12 ml per kilo group, most patients who are randomized had to have their tidal volume increased, increasing their pressure.

So let's look at what the randomization looks like.

We'll take the two groups and just randomize them.

So the low group, the people on low tidal volumes who had a significantly increased severity of lung disease, was randomly assigned to 6 and 12.

Likewise, the ones on high tidal volume with more compliant, less severely injured lung were randomly assigned.

In particular I want to focus on the fact the patients with non-compliant stiff severely injured lung, that half were randomized to large tidal volumes that their physicians would not have put them on, resulting in high airway pressures; airway pressures that would continuously set off the alarms on ventilator, as a ventilator is normally set up.

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This is the results of the trial. As you can see, there's a very consistent effect over time. Very early in the trial, there were differences between these arms.

Raising tidal volumes to 12 ml per kilo resulted in more deaths than lower tidal volumes to 6 ml per kilo. But like SUPPORT and a lot of other trials in this trial type, there was no usual care arm.

There was nothing in this trial that represented standard care. There was no proper control. When the data safety monitoring committee looked at this, they continued the trial because they thought the 12 ml per kilo represented usual care. But as I just showed you, it didn't.

Once assigned to that group, physicians would not have continued to titrate your tidal volume down as lung injury changed and became more severe during the trial.

So let's try to formulate, given this trial is not done the way I think it should have been done.

What was usual care?

What was the result of usual care?

The only thing we can point to is mortality rate in screened but not randomized patients.

That was again similar to the 6 ml, the experimental arm, and very different than what was continued -- the control arm.

If you had had a control arm and it looked like in the trial, that trial would have been stopped with less than 200 patients in it.

Instead the trial continued and people in the 12 ml arm continued to die in excess of those in what I think was standard care.

Looking quickly at those patients screened and not involved, you can see a variety of reasons that they weren't in the trial.

But there's an incredible consistency of what the mortality rate is in those groups who received care as their physicians gave it.

So in conclusion, uncoupling care from an individualized approach may indeed cause harm.

Routine care arms are necessary for safety monitoring and valid basis to inform current practice.

Randomization to both ends of usual care treatment range, particularly in critically ill vulnerable patients, has risk and is not equivalent to non-research care.

Thank you.

MODERATOR:

Thank you, to the panel now, OHRP.

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JERRY MENIKOFF:

Thank you.

No questions.

MODERATOR:

FDA?

ROBERT TEMPLE:

Would you think with respect to more study that physicians would adjust oxygenation levels in response to certain signals?

Is that something that seems plausible?

ROBERT DANNER:

Yes, I think it seems very plausible.

I think the saturation - first of all, the physician is adjusting FiO₂ and the saturation is just the result of that adjustment.

So depending whether you're starting out at high or low FiO₂, you may in somebody on higher FiO₂, because you know it's dangerous, accept a lower saturation; whereas someone on low FiO₂, you wouldn't push to higher, unnecessary saturation as was pointed out by Dr. Natanson.

In addition there are many other parameters that randomization takes out of those adjustments.

If you have a child with perfusion who has a rising lactate you may want to give that child more oxygen so they have better oxygen delivery to their tissues because you know if you don't perfuse the organs that child is going to develop multi-organ failure and potentially die.

You also might have bloody diarrhea, suggesting that the child is going to get necrotizing enterocolitis which case you may want to run higher.

Likewise, there are similar reasons for wanting to run FIO₂ and saturations lower in a patient.

And all of that is taken out by randomization.

ROBERT TEMPLE:

Oh, sure. Have people looked at care of infants to see what physicians actually did?

Along the lines you're talking about; it certainly seems plausible.

There's literature what people do and what they recommend.

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And I think that proposal, before you enter a study like this and maybe even before an IRB can make reasonable judgment of what the burdens and risks are, you actually have to ask that question and find out what doctors are doing and why they're doing it.

MODERATOR:

NIH?

KATHY HUDSON:

Thank you, no questions.

MODERATOR:

Excellent.

Thank you.

MODERATOR:

PowerPoint slides again.

Nancy Kass, thank you.

PRESENTER: NANCY KASS

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NANCY KASS:

Thank you.

So thank you for organizing this hearing and allowing us to give input into this challenging issue.

Before I start my prepared remarks I want to read two claims that I feel I have heard throughout many presentations this morning both of which I hope to challenge a little bit in my own comments.

First is the claim that individualized care is by definition better than care received through a research project.

Secondly, that research using FDA-approved and commonly used therapies, should have identical oversight as research using investigational or experimental or non-FDA approved therapies.

So I'm going to start by outlining a historical premise on which our regulations are based about how research and care differ from each other, and then I'm going to offer two reasons -- there could be a lot more -- why there could be a lot more, following from the premise why thinking about standard of care research and I will also use the language in the Federal Register, within our current regulatory structure becomes challenging.

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Then I will close with a couple remarks about ways forward.

Here is the historical premise:

Most of us are taught to think of research and clinical care as two different enterprises. Both conceptually and morally.

And that distinction has been put forward in the way we treat our public policy.

Conceptually, we have been taught that research is where we have uncertainty and where we're trying out new approaches and learning new things to apply in the future to the care of other patients.

It's what was called nearly 40 years ago, an intent to produce generalizable knowledge. And by contrast with clinical care conceptually, is where we apply what we know to the care for the patient in front of us doing best for the patient and concerned about the patient's own well-being.

So morally this distinction becomes very important.

Because if research is designed to help other patients, we might expose the patients who join research to more risks or uncertainties or burdens, than if we were only thinking about their own well-being.

Therefore, we must provide them with reasonable oversight and obtain permission from them to be part of the enterprise.

Morally, let me underscore the idea that people who might be exposed to more risk or burdens, or have important interests compromised, deserve additional oversight or conversation -- is a completely sound idea ethically and that is not the idea I wish to challenge.

Carrying the logic of the historical premise to clinical care, we can conclude since we are applying our best knowledge to individual patients' medical problems, then whatever risks they endure are simply reasonable trade-offs they must make for the clinical benefits of those needed treatments or interventions.

Because we aren't asking them to contribute for anyone else, we don't provide additional oversight or protections and we don't necessarily engage in a lot of conversation about options, risks, or alternatives, or at least not in any formalized or systematized way.

Why does this become problematic when we then move to the context of what's been called standard of care research, or comparing different standard treatments?

I'm going to focus only on two pieces.

First of all, this historical approach has created very different norms, whether or not it ought to be this way, it has created different ethical and professional norms about disclosure when we have a patient in front of us.

When we bring the clinical research worlds together within the same activity, when we want to learn in rigorous ways, about approved standard treatments, there is at very least confusion about what has to be told and more than that, they've created different kinds of concerns and possible expectations.

Secondly, our regulations were intended to provide ethical protection for research participants, again based on assumptions that they're being exposed to more risks or burdens in research than would have not been in clinical care. And yet for many types of research, including standard of care research, these assumptions may often turn out to be faulty.

Let me start with first one about ethical professional norms about disclosure.

In clinical care, we assume doctors are doing their best and we rely on them for their professional judgment, and that's a good thing.

We don't require them to tell patients again often, at least in any systematized way, or in ways for which they're accountable, about alternative treatment approaches, when they may be available, the relative risks and benefits of what they're recommending versus these alternatives, the likelihood of getting alternative approach if they went to a different doctor or hospital. And of course many doctors disclose some of this information but many do not.

And it certainly is not the norm for treatment risks and alternatives to be written down or signed or reviewed by anybody else.

In clinical care the norm is, doctors tell us what treatment they think is best and even if they mention risk they quickly describe how these are part of the package of getting treatment we need.

But in research, we set norms, standards, or widely used therapies, which must be accompanied by lengthy discussions of risks and alternatives. Because no guides exist in regulations regarding how to characterize the risks or compare commonly used medicines which many of us would assert are different from other kinds of research risks, researchers and IRBs generally default to describing all the risks and benefits of the therapies as if they were new experimental therapies rather than describing additional risks, if any, of the research or learning itself.

Ethically it cannot be defended that we have such different standards for when patients deserve to be given information by trusted healthcare providers about whether their recommended treatments are risky.

Or how risks and trade-offs compare across alternatives.

Certainly, it's at very least ethically confusing that patients must be told about risks when we want to learn about care.

But we don't have to tell about risks or alternatives if we don't care whether or not we learn.

So second, research regulations are based on the sound ethical premise that there should be more ethical oversight and stricter thresholds of informed consent when patients are exposed to something very risky or burdensome, or might compromise important interests that they might have.

If we expose someone to risks or burdens beyond those needed or expected for their standard care, then ethically there should be more discussion with them and more independent oversight.

So the faulty assumption comes with public policies that suggest additional risks and burdens, and compromises happen uniformly in clinical research.

The default is we must assume this happens in all types of clinical research and thus research participants need the same types of protection, but by definition these additional or added risks and burdens don't happen in clinical care.

Whether patients enrolled in a standard of care study are exposed to more risk than patients receiving care outside of studies is a commonly made claim and it's compelling, but it's an empirical question.

MODERATOR:

Your seven minutes are up.

NANCY KASS:

Okay. Thanks.

Studies to date suggest that patients enrolled even in experimental trials fare no worse than patients outside of these studies.

Let me just...

I'll conclude by saying that intuitively, for most of us who are raised to understand what a culture of good research means, it may seem antithetical to what we have learned and internalized.

To say that we shouldn't disclose every possible risk to patients, but treating all clinical research the same way also risks our sending a message to patients...

MODERATOR:

Please wrap up.

NANCY KASS:

That standard of care research is riskier than usual care they would have received.

MODERATOR:

Stop. Thank you.

To the panel. NIH?

KATHY HUDSON:

I get the sense you didn't quite get to the end, so I was going to ask what was the end because you talked about...

NANCY KASS:

Kathy, you're my friend!

KATHY HUDSON:

I think that the work that you describe, the thoughtfulness of your remarks were incorporated in a very helpful Hastings Center article recently, is that true?

This notion that ordinary patients are getting less than research participants, struck me profoundly in the SUPPORT study in talking to friends and family members who had extremely premature infants where they were never told what oxygen level their babies were being put on.

They were told very little about the care that was being delivered to infants, whereas the SUPPORT study and research in general, an expectation of a higher level of transparency.

So I'll make that as a comment.

In terms of our paths forward, what would be your suggestion about how to move forward?

NANCY KASS:

I appreciate your comment and I'll take the assumption that this group doesn't have the authority to make any public policy with regard to clinical care, much as there might be recommendations that more disclosure should happen.

I do think that it's important to think about how levels of risk differ in different kinds of research studies.

And how those levels of risk compare as best we know to what exists in standard of care.

If we can use a risk threshold that is relative to care and of course relative to other kinds of research, then maybe what we disclose could be titrated to what we think the additional risks are.

I don't think any of us want to say we should stop talking to people.

If that's the message, I'm not stating it correctly at all.

But we end up misleading people.

If we talk risks in an extreme way in one context where actually the risks are not greater than other contexts where we don't have the same kinds of discussion.

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MODERATOR:

FDA?

ROBERT TEMPLE:

In one of these studies comparing two things that are considered typical or standard of care, the risks you're looking for are really the point of this study.

It's to see whether one treatment is better than the other.

If you're randomized to the one that turns out worse you might do worse, there might be components going in different directions.

What always struck me is the point of that study is to find out that thing, and I don't want to oversell the idea that physicians know what they're doing. But when a physician just treats, the physician presumably is uninfluenced by anything.

May not be true, but leaving that aside.

The physician is making the best of a bunch of choices and there's no question in mind.

He's not trying to find out anything.

So the idea was, has always been, if you're the subject of a study, where the point is to find out something, you should be told about that because that's a different environment from your doctor just trying to do the best for you.

Are you saying we're over-doing that, that when you're comparing two treatments in widespread use, we don't want to overdo the possibility that they might be different or what?

That is, after all, the whole point of the study.

You wouldn't do it but for the thought that they might be different.

NANCY KASS:

Absolutely.

I appreciate the question.

So no, I'm not at all saying we shouldn't tell people that the point is to compare which is better.

But I think we also want to say, had you not been in the study, you would have gotten one or the other without knowing whether it was the best treatment for you.

The other thing that your question makes me think of, is that while we focused a lot today on informed consent, arguably some of the best protections for the patients in that study have to do with the design rather than the consent.

If eligibility criteria limit patients to those where reasonably they might have gotten either of the therapies, that is a protective mechanism and you never put someone in the study who might not have gotten therapies.

More have switching rules so if patient isn't doing well they can change.

There are lots of ways to protect patients from risks in addition to telling them drugs can do bad things to them.

MODERATOR:

We're almost out of time. OHRP?

JERRY MENIKOFF:

Thank you, Nancy.

So as you indicated in other context, your Hastings center report article basically is a fairly radical rewriting of the current system, at least that's the way you positioned it in many other talks, including your colleagues.

And again, I personally support letting our society have this debate.

But getting back to current rules as Dr. Temple noticed, we currently expect in the clinical encounters that doctors make their best judgments for what they think is good for us.

Even in the face of uncertainty, maybe that doesn't always work, there are bad consequences sometimes, again in the current system in the research setting precise because we're altering somebody's care, we expect greater disclosure and maybe we should change the rules.

Small scenario: Two drugs, both standard of care, both used for a particular treatment, become concerned for various reasons, whatever it is, one has increased risk of death.

Propose the study by which you randomize people between those two drugs.

Under the current system it's reasonable when we tell somebody you get consent we tell them by the way, the reason we're doing this study is that we're concerned that drug X might have an increased risk of death.

Not sure, but that's exactly what we're studying.

If we claim consent and I accept maybe you want to tell me no need for consent any more, why isn't it required to basically be telling people if we intentionally move them to a particular treatment, this is the concern we have about a particular risk of that treatment.

Why isn't that basic ethics?

NANCY KASS:

I want to make sure I understand, are you saying why would one not do informed consent for a trial like that?

JERRY MENIKOFF:

We don't need consent which I understand you're making some utilitarian argument that we would learn more by not getting consent. But if we want consent -- this is like SUPPORT again -- you're intentionally changing the treatment somebody gets to move them to particular type of treatment where you're concerned about a particular risk and the basic point a lot of people, including OHRP, you should disclose the risk when part of the study is randomizing to that risk.

And maybe you agree with that in which case it sounds you're not disagreeing with OHRP.

KATHY HUDSON:

I think the difference there is, in your example, there was...

MODERATOR:

We're getting a lot of feedback in the mics. Did you cut us all off?

KATHY HUDSON:

Your suggestion was that there was data to support...

JERRY MENIKOFF:

The clinical community is concerned for appropriate reasons. Let's not get into data.

Could be physiology, whatever else.

KATHY HUDSON:

Concern and data, differ.

MODERATOR:

Did you want to give a 30 second distillation to give you in fairness, in response to any of that, or throw up your hands and say more later? Your choice.

NANCY KASS:

The one comment I'll make is to echo part of what John Lantos said, which is, we mislead people if we suggest that it is through research that they might be exposed to an additional risk.

And we don't include even in a research form the possibility that they might have gotten either drug which we don't know which is better, either of which might have been better or worse for them.

Thanks.

MODERATOR:

Excellent. Thank you.

I apologize for the feedback in the mic issues.

At least for us at the table it was pretty awful or maybe it was just me.

We are at -- we have actually 10 bonus minutes for lunch.

So we will start again promptly at 1 o'clock.

Looks like a little bit of sun outside, I really encourage you to check out the Fresh Market outside -- options you can have your lunch for about 10 bucks.

You won't save money going to the cafeteria, you might save a little bit going down near the Metro.

Your call, but quite a few options in the area.

See you promptly at one o'clock.

Thank you.

BREAK FOR LUNCH

MODERATOR:

Folks, please take your seats.

We are ready to get started with our afternoon slate of presenters.

For those who were not here this morning, first of all, for security reasons, you have a blue badge if you're not a federal employee; you have a blue wrist band.

You will need to be accompanied or whatever over the restrooms.

The restrooms are over that side of the building.

And if there is a need to go to the cafeteria, you will need to be accompanied with someone with a federal badge, an HHS badge.

And if you need to take a phone call, have your phones on mute, on silent on vibrate, whatever.

Take your calls outside, at least past the screen back there so that the meeting itself is not disrupted.

We were grateful to the presenters this morning who were fabulous in staying on time.

We have had some lively debate.

And you know we wanted to hear all points of view.

And that is the purpose of the meeting- and are getting there; and we are really getting there.

We appreciate that.

So we think the afternoon will be no exception.

I believe it was 14, I counted them once and I have forgotten.

We have a number of speakers this afternoon.

First are Jeffrey Drazen, Peter Vasilenko, Steven Joffe.

The next three: David Forster, David Magnus, and Carl D'Angio.

The next three: Jon Tyson and Michele Walsh and Shawn Pratt.

The next three: Sharissa Cook, Edward Campion, Michael McGinnis

And the last three: Richard Platt, Ann Bonham, and Robert Califf

And I hope that I have pronounced your names correctly. I know you'll correct me if I mess up when I bring you up.

So we are ready to start.

Jeffrey Drazen, please. And – here we go. No slides. Great, thank you.

PRESENTER: JEFFREY DRAZEN

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JEFFREY DRAZEN:

Thank you and good afternoon, everyone.

I'm Jeff Drazen.

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I view myself primarily as an active physician and sort of secondarily an editor.

So when you seek medical care, your provider has to make many decisions.

His diagnostic setting, what test to order, in a therapeutic setting, it's what treatments to give, and in standard care settings, it may be something as simple or complex as what screening tests to do.

And for many of these decisions, we have absolutely no data.

I just finished a brief period working in our intensive care unit at the Brigham and Women's hospital and I counted every day, over 50 questions for which the answer could have been given by a flip of a coin.

We need to do better than that if we are going to improve our health care system.

There needs to be a way to address things that we commonly do to determine whether there is one better way that is better than the other.

And there are lots of settings for this, some of which may seem surprising.

Consider a study published in the New England Journal of Medicine, one of my favorite medical rags, that compared two different preparations used for cleaning the skin before surgery.

One of them, providone-iodine was developed at the Brigham during World War II and the other was a newcomer, chlorhexidine-alcohol.

And before the study was done, these two skin preparations were considered to be essentially equivalent.

But a study was done and informed consent was obtained to compare the outcomes of having your skin cleaned with providone-iodine vs. chlorhexidine-alcohol, looking at the incidents of surgical site infections, postoperatively.

And to every one's surprise they thought they would be pretty much the same.

There were more infections with the providone-iodine than with the chlorhexidine-alcohol.

So as a result of this work, comparing two treatments that could be considered standard of care.

Now George, I don't want you to worry about this.

Standard of care to me is easily defined.

When my kids were little, I'd say, the standard of behavior is standard behavior and I'll know when you're violating it.

Standard of care in a medical setting is the same way.

Doctors who do things that are generally accepted by the community are a standard of care.

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Unfortunately, we don't often keep meticulous records about what standard of care is, which may lead to many arguments about it in an ex post facto sort of way.

When we are looking at things that are standard of care, I think most people understand what that means.

Since we have to make decisions every day on which we have very little data, we do what feels right to us or what we learned at the time of training.

But we know from the behavioral research, that you're more likely to do what - something based on your recent prior experiences.

So imagine you're a surgeon and the last case you did had a skin infection, and you had cleaned that patient's skin with chlorhexidine-alcohol.

So you're next patient, you're going to say, that wasn't good; couldn't have been my hands.

As a surgeon, I'm going to switch to providone-iodine.

And you probably watch all your patients until you have a couple of in a row that had an infection with that and then you switch back.

For this particular case, we have data, we know.

We go from something we think, to something that we know to be able to make an informed decision.

And that is what this meeting is about.

It's about doing research to improve what we do in many, many things on a daily basis.

So, this has led, this desire to improve outcomes has led to research studies that compared diagnostic approaches or therapeutic regimens or processes of care in which each intervention is considered to be essentially the same.

One may be more costly, one may have -- may hurt a little more, but have better outcomes in the long run -- we don't know.

What a physician does when he or she makes judgments in the process of care, is they try to customize, but I think it was put most eloquently by Dr. LANTOS earlier; we are just guessing.

And his grandchildren are the result of those kinds of guesses.

When we do things that are protocolized, we do better.

It's been shown over and over again.

If you have a roadmap to follow, you're way better off than if you're wandering around without one.

So it's my premise that settings, it is to determine what is best among things that are considered standard of care.

The researchers proposing the work need to study the area and prepare the document outlining the research trial showing what is known.

Now, for most of the things that we are going to be looking at, there aren't going to be randomized control trials looking at A versus B.

There may be some observational data which we know is highly likely to be biased, and there may also be expert opinion.

But there probably isn't going to be gold standard evidence on which to base our decisions.

But these people, the people proposing the work, the onus lies with them to write out what the question is and why they think clinical equipoise exists.

Now Jerry, here is where I think we need to do something different.

Right now that proposal goes to a bunch of different IRBs.

I think that there should be an IRB convened specifically with expertise to look at the question that is being asked.

And once they have read and said yes, clinical equipoise exists and the method that you're using to address that question doesn't contain excess risk for the people in the population, it is well laid out.

We then say, yes, it has happened.

At this point in time, equipoise exists.

When we look at the SUPPORT study, and we spent a lot of time arguing about the SUPPORT study, to me the biggest problem is where we can't put ourselves back where we were in 2003.

MODERATOR:

You're seven minutes are up.

JEFFREY DRAZEN:

So to get there, we need to have an IRB that knows why the study was being done and how it is being done.

Thank you.

MODERATOR:

Thank you.

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Now to the panel.

FDA?

ROBERT TEMPLE:

Your last comment actually intrigued me. At least a decade ago, we said that central IRBs were okay and you didn't need more than one for a study.

England's sort of giving everybody a central IRB.

But our understanding is nobody likes them here.

Do you have any particular insight into why that is?

JEFFREY DRAZEN:

So I don't think the local folks like to give up local control.

So in my idea, there would be a central IRB that would approve the study design and that equipoise exists.

But that the local IRB would be involved with the making sure the researchers are in fact qualified, and that the informed consent is appropriate for that community.

Because when we were doing Asthma studies, the appropriate informed consent in Harlem was different than it was in San Francisco.

ROBERT TEMPLE:

So you could do that now.

Would you have thoughts about how to encourage that behavior?

JEFFREY DRAZEN:

So, the way I would encourage that behavior would be -- the OHRP to say, let's use a central IRB to define the question, define clinical equipoise, and then move forward.

Because looking backwards as we have done with the SUPPORT study, I think it is just fraught with difficulty.

So we need to go forward, not backwards if we are going to make progress.

MODERATOR:

NIH?

KATHY HUDSON:

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Thanks.

So, your proposal for a specific IRB is not that different from the recommendation that an IRB consults with appropriate expertise in order to make a determination of whether or not research within the standard of care does really achieve that balance; really does achieve clinical equipoise. Would that be another --

JEFFREY DRAZEN:

I think there are different flavors of the same thing but not very different flavors.

KATHY HUDSON:

Thank you.

MODERATOR:

OHRP.

JERRY MENIKOFF:

Thank you Dr. Drazen.

I certainly appreciate the comments about central IRBs and more broadly, the purpose of this meeting is in fact to make sure that everybody understands what the rules are going forward.

So, in terms of -- let me ask you one question, clinical equipoise tells you it's a legitimate study; that it is appropriate to do this study.

It doesn't answer the question about informed consent and what people should be told.

You could have clinical equipoise but there can still -- can't there be legitimate reasons why somebody might want to take one arm or the other arm as their treatment outside of the study and we are back to what should you disclose in terms of if, in fact, the physicians community out there is concerned about a particular risk; shouldn't that be disclosed?

JEFFREY DRAZEN:

So, what if the -- if the IRB argues that clinical equipoise exists and sometimes it is full equipoise and sometimes there may be compelling arguments one way or the other.

One treatment may be more effective but more toxic; the other treatment may be less toxic but less effective and trying to see which gives longer life, for example.

But I think that with respect to the issue of what you tell patients, I think that you should tell them what the question is and how you're proposing to answer it, rather than couching this in the language of panel A or intervention A has this risk and intervention B has that risk.

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Rather, lay the question out and then explain how you're proposing to answer it.

And I think that will get to this issue.

JERRY MENIKOFF:

Thank you.

MODERATOR:

Thank you.

MODERATOR: Peter Vasilenko.

PRESENTER: PETER VASILENKO

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PETER VASILENKO:

Good afternoon.

I have just two brief comments and subsequent suggestions based on looking at the SUPPRORT consent forms as well as probably hundreds if not thousands of other consent forms.

My first point is that, I heard a lot this morning about the blurred line between care and research.

Reading consent forms, I'm not sure I see a line most of the time.

I think we do a very poor job of actually differentiating in any particular consent form, what is being done for research purposes and what is being done – or would happen anyway outside of the research context.

This morning there was the discussion about what would happen if an infant wasn't in the study.

And would it be high or low or in the middle?

I'm hoping that somebody knows the answer to that question for that particular clinic, what would be done.

And why wouldn't that be in the consent form, then?

When I talk to physicians about this, and particularly physicians that are at a performance site, they didn't invent the trial, didn't develop it but just performing it, they have a very difficult time trying to tell me, and certainly in consent form, what is being done for research purposes and what is being done as part of normal care.

Just last week I heard somebody referring to clinical performance science and saying, we offer clinical trials because we want to increase the number of therapies we can offer our patients.

It's being looked on as therapy so obviously they will have a hard time distinguishing it from what is research.

In addition, the consent forms are weak on the specifics of alternative treatments.

They say things like, you'll get the usual care that is offered at this clinic.

Which gives somebody absolutely no basis of making a comparison to specific things that are in the research.

Or in the consent form.

So I think that -- I just wanted to mention, in looking at oncology clinical trials, often an alternative treatment is another clinical trial.

So it's really hard for those people to distinguish what is research.

Is there any treatment outside of the clinical trials?

So the IRB should consider whether the differentiation between standard of care and research and in the consent process is sufficient.

Consent process and document is sufficient.

And I think IRBs should be a little more critical in saying that I don't understand and I think you should clarify that.

This is my suggestion here that we actually draw a line, a white line in this case, and say, here is what is being done for part of this study.

Here is what is being done for routine clinical care and if you don't participate, here is what you would get.

This way, the person could look at this and say, now I understand exactly what the research is adding and I could make a informed decision about whether I want to do that or do the alternate treatment.

This gives them the information to do that.

Just as a suggestion, actually puts in a line.

My second point is, if you notice Dr. Hudson in her comments this morning, twice said that the research risks should be looked on in terms of the baseline risks of those, in this case, infants.

And this is my second point.

We need to consider the research risks in the context of those baseline risks for population, whether prisoners, combat soldiers, premature infants, NFL football players when you're studying concussions.

The baseline risks are different than the general population and undoubtedly impacts the outcome with or without the research.

Consent forms are weak on the specifics of baseline risks and putting the research risks in the context of the normal risk that you're in.

And the IRB certainly needs to be aware of those risks and think about those risks when they think about the research risks.

I think IRBs shy away from that because of the issue with the definition of minimal risk and you're not supposed to think about prisoners or soldiers or something when you're determining minimal risk.

That is kind of spilled over into our thinking overall so we never think about it.

But it certainly, when -- I'm going to give you an example that brings this to light in a second.

Maybe more controversially, I think that subjects or parents of subjects should understand these baseline risks in order to understand the increase or decreased risks or how big or small they are and the research may offer. I realize in a situation with premature infants when you're talking about mortality, you're talking about a very difficult situation when dealing with parents.

But, you've seen the oxygen levels all over the place.

I want to show you the mortality data.

This is from, I just pulled this slide from a paper I presented in 2002.

Unfortunately, the -- it hasn't changed much in the last 11 years.

But you can see that between 24 weeks of gestation and 27 weeks, which was the support study, where that---how high that mortality is.

In 24 weeks you're talking about 55%.

I didn't say, this is a large data source from a Midwest population.

So this is the context that that study is being done in.

With these mortality rates, regardless of the research.

This has nothing to do with research.

And these percentages of infants are going to die.

You could do a chart like this with retinopathy of prematurity and reticular hemorrhage.

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Learning disabilities at eight years of age.

And then you will have a context to tell people about the research risks in relation to the actual risk that they are going to get or have regardless.

MODERATOR:

Your seven minutes are up.

PETER VASILENKO:

And I'm up.

So I'm done.

Thank you.

MODERATOR:

It means you're up.

Panel.

Let me start with OHRP.

JERRY MENIKOFF:

Thank you.

No questions.

MODERATOR: FDA?

ROBERT TEMPLE:

I'm afraid I don't either.

Thank you.

MODERATOR:

NIH.

KATHY HUDSON:

Thank you for a clear presentation.

I think your table of what is a part of research and what you would have gotten otherwise is very helpful, although it doesn't get to the issue of what are the additional risks and benefits of each of those elements in the table.

So would you anticipate that would be a subsequent pros-based discussion?

PETER VASILENKO:

I thought of that and you could do a similar thing for risk, not just where the procedures are.

And actually, I think this would shorten consent forms because you could put a lot in a table rather than many paragraphs of text.

Thank you.

PRESENTER: STEVEN JOFFE

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MODERATOR:

Steven Joffe is our next presenter.

STEVEN JOFFE:

I'd like to thank the Department for allowing me to comment on one of the many important issues that have been raised in today's meeting.

I'm going to pick up on the theme that was echoed in the last talk, part of a discussion between Dr. Temple and Professor Shepherd this morning, and also implicit or explicit in recommendations that Elisa Hurley offered on behalf of PRIM&R.

And I'm going to end with one fairly concrete request and proposal to the Department.

My comments focus on an ambiguity in the Common Rule definition of minimal risk.

I specifically want to request that the Department clarify that ambiguity and provide guidance that harmonizes the definition of minimal risk with the approach to risk assessment specified in section 111 of the Common Rule, which outlines the criteria for IRB approval of research in the first place. If the Department agrees with the interpretation that I will offer, then I respectfully ask they issue guidance to that effect.

Clarification of this ambiguity would be enormously helpful to individuals seeking to study standard of care interventions or interventions commonly used in the course of medical care, in clinical practice, and to the comparative effectiveness enterprise more broadly, I would add, in my view, without in any way compromising the rights to safety of human subjects.

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So according to section 102 of the Common Rule, which many are familiar with, minimal risk means the probability and magnitude of harm or discomfort, anticipated in the research or not greater in and of themselves but those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

It's not clear at least to me and many of the people with I have spoken about this, whether or not the risks of standard care interventions that are embedded within a clinical trial, obviously we were talking about intervention that is participants would likely receive even if they didn't join the trial, should be counted as risks that are quote, "anticipated in the research", a key phrase in the definition.

I'm also unaware of guidance from the Department that addresses this question.

In my view, an IRB considering how to apply this phrase might reasonably conclude, although I don't think it would have to conclude, the risks of standard of care intervention should be viewed as risks of research.

Yet based on the criteria for IRB approval of research in section 111, as I will describe below, I believe this would be a mistake.

So moving to section 111, the section that describes the criteria IRBs must use.

One criteria must verified before approving research, "risk to subjects are reasonable in relation to the anticipated benefits if any to subjects, and the importance of the knowledge that may reasonably be expected to result.'

And here is the key phrase.

"In evaluating risks and benefits, the IRB should consider only those risks that may result from the research as distinguished from the risks and benefits of therapies subjects would receive each if not participating in research."

So in deciding whether to approve a study, IRBs should say these are the risks subjects would likely receive outside the study, we're not going to count those in our risk benefit balance with respect to the study, we should think about only those risks that are added or brought on because of the study.

This paragraph makes clear that IRBs should consider only incremental risk of research over and above those of standard of care interventions when deciding whether or not to approve a study.

And my request is the logic be carried over to the definition of minimal risk where I think at the moment it's ambiguous.

I would like to propose, and here is my specific request and recommendation, that the same logic should apply to decisions about whether or not a study involves minimal risk and to request that the department issue guidance to that effect.

This guidance can state simply, really just paraphrasing the statement a moment ago in evaluating whether a study involves minimal risk or greater than minimal risk, the IRB should consider only those risks that may result from the research as distinguished from the risks of therapies subjects would receive even if not participating in the research.

Thank you.

MODERATOR:

NIH?

KATHY HUDSON:

I don't have questions but I appreciated your remarks, thank you.

MODERATOR:

OHRP?

JERRY MENIKOFF:

Thank you Steve.

This is a great point.

Let me just try to see if I understand what you're saying because in terms of just reading your statement, it sounds pretty much like personally I agree with it and there are -- I don't want to say as a regulatory matter what you actually have to put in in terms of background risks.

In fact there are currently discussions with NCI about its template and I'm sure on behalf of the -- in terms of to what extent you could not have to say this stuff.

But just to ask for clarification, when you say distinguished from risks of therapies they receive even if they were not participating in the research, I take it you're not saying that had you not been in the research you were going to get point X in the range of standard of care but in the study they randomized to you points Y or Z.

You're acknowledging that there should be some discussion of differences between X and Y and Z?

Yes?

STEVE JOFFE:

So I was not, although the issues I raised are important for what does or doesn't belong in a consent discussion or form, I was actually trying to speak to the issue of what is or is not a minimal risk study.

That said, in the situation that you're talking about, I think yes, transparency about the sorts of issues, but what are the differences, if there is variation between what you will get in the study and what you OHRP staff created this transcript from the video captions by correcting transcription errors and identifying the speakers.

would have gotten or might have gotten outside of the study, I think a level of transparency about that is appropriate.

There is a different question about, as you know, there are many decisions that hinge upon whether an IRB determines a study is or is not minimal risk.

I'm saying this sort of reasoning might help to make those decisions, something as simple as would a study qualify for expedited review.

JERRY MENIKOFF:

I think you make a great point, and stated your point very well.

But I appreciate some people might have been implying that you were saying as long as it's part of standard care, even if it's in different places in the range of standard care, that automatically meant none of those get considered and your clarification is very helpful.

ROBERT TEMPLE:

I think it is helpful.

One problem, I think, I'm not positive about this, fortunately, correct me if I'm wrong, FDA doesn't have that 111 exception as it applies to HHS rules.

So minimal risk may well include all the risks of the whole deal unless we do something to say that that can be changed.

A good example is the study that Dr. Drazen described, where you're smearing on two different antibiotics.

Maybe they have some risk of irritating the skin on their own, but clearly being in the study, you get the usual risks and you don't know of any additional risks at all.

So you really would think, that sounds minimal risk.

I'm not sure we can do that now.

But it's on our mind.

We are thinking about it and we are not unsympathetic to your view, at least I'm not.

STEVE JOFFE:

Great.

Thank you.

MODERATOR:

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David Forster.

PRESENTER: DAVID FORSTER

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DAVID FORSTER: So, it figures I come up after Steve, who, no one has mentioned a regulation until just now and Steve does and that's what my slides are.

So I like the way he thinks.

I want to point out first of all that HHS asked for comments on how an IRB should assess the risks of research involving randomization to one or more standard of care interventions, and what reasonably foreseeable risks should be put in the consent forms for those studies.

And this is a problem much broader than these types of studies.

It is a problem across all of the research regulations and all the types of research we review.

Risks and benefits are mentioned many times throughout the regulations.

And we have very little direction from the agencies on how we are supposed to categorize and find those.

And as a result, IRBs, investigators and the agencies themselves, vary on how they interpret them.

And I think if you look at the literature, you'll see risk assessment, net risk, accumulative risk and differential risk, relative risks, and absolute risks.

We are all using slightly different formulas for how we think about this.

So, these requirements for assessing risk and benefit go across all these various sets of regulations, including FDA, and so what I would like to propose is that there be guidance from the agencies that is consistent in how we classify and assess risks and benefits of research, all research, and how risks and benefits are presented to subjects in the consent form.

And this guidance should be applicable across the regulations.

And I want to point out where I think a lot of the confusion comes from, and Steve just showed this slide.

But in evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.

And then, you get to the consent regulations.

Slightly different language.

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It says you need to in the consent form, provide the description of any foreseeable risks or discomfort to the subject, and any benefits to the subject which may be reasonably expected from the research.

And here is where I think we get our confusion.

We all or many of us interpret differently the concept of minimal risk, risks and benefits that may result from the research, and risks and benefits of therapies subject receive even if not participating in the research.

Some is minimal, some is not.

We are just not clear in how we correlate those terms, and that is where I think most of the difference comes from in our assessments.

So I would like to propose that we have a systematic classification.

Now David Wendler says your theory won't be accepted if you don't have a catchy name. This is not that name.

SCARB. I tried.

But what I'd like to say is we go through and first identify, in a systematic way, what is not a research risk or what is a research risk.

Then analyze the risk benefit ratio of what is a research risk, and then decide what goes in the consent form.

If you're systematic about that, there would be more congruence across various IRBs in the outcome.

So, what should this guidance look like?

I think it should provide a clear direction on where you start on those assessments, because it is very often in research that we have a standard of care arm, whether placebo-controlled trial or investigational drug or involves children, where we have extra risk benefit ratios to consider.

And so we need to know where you start in that assessment.

Where you launch from.

It needs to be applicable across all regulations and most importantly, it has to be broader than just medical research; for instance, the CHEER study which studied pesticide exposure. It needs to apply to behavioral research.

So on the topic at hand, what risks of standard of care should be put in the consent form?

I would say that we would want to put in anything where the subject environment is altered by research methodology.

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Here is where I'm going, from where it sounds like a good idea, its general idea here is a proposal that will make half of you mad.

It's where I think we can draw a nice clean line and you know, if your only research methodology is a collection of data then don't put the other risks in the consent form.

A nice clean line.

The reason I like the clean line like that is it is simpler for somebody from the regulated position and it provides a nice transparent goal for the public, for Congress, for others to say, here is what they are supposed to be doing.

It's simple.

And given the debate over this particular study, I think that something that is transparent is a good idea.

Let's move towards transparency in this debate that has caused this much concern.

This also provides a nice clean line for defining registries versus Phase four studies, a very confusing issue on the FDA side, and I would say that if it is a registry, the definition of a registry is the enrollment, research occurs separately from the clinical decision to use a regulated product.

But if the enrollment in the research involves the decision to put the subject on that particular drug or product, then it is a Phase four study, and you don't have to put the risks of the product in registry studies but you do have to in Phase four studies.

The reason I say that is the distinction of the timing and purpose of the decision of when to put somebody on the product, whether clinical or research driven.

We don't focus on it very much, and you don't see it in protocols.

I look for it all the time.

It's hard to assess the difference between a registry and a Phase four study on those decisions, and I think it has ethical weight.

I'd like FDA to agree with me.

As to the SUPPORT study, if you follow this logic, the risks of the inventions would have been in the consent form.

And I want to finish with two thought experiments.

Let's say you have a study, a comparative effectiveness study and then in the middle of the study a new risk pops up.

Do you not tell the subjects because it's not a research risk?

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If you do decide, we are going to tell you about this new risk, do you still ignore all the other risks of the drugs they are on even though they have been randomized across those drugs?

Interesting question.

And I think a second one, same situation.

Comparative effectiveness randomized trial and you randomize people and the DSMB shuts down the study because one arm is better than the other.

So now you haven't told the subjects that there is research risk here, and all of a sudden, the DSMB shuts down the study and says one arm is particularly better and one is particularly worse and you happen to be randomized to the worse.

That's difficult, I think.

So that's where I'll finish up.

MODERATOR:

Perfect.

Thank you.

And to the panel, OHRP.

JERRY MENIKOFF:

Thank you, David.

And it's really helpful the way you lay out these particular questions and that they are specific enough.

That's useful.

MODERATOR:

NIH?

KATHY HUDSON:

I don't have any questions, thank you.

MODERATOR:

FDA?

ROBERT TEMPLE:

We already do say that Phase four studies are clinical trials if they are randomized control trials.

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I mean, they have to meet all the usual requirements.

Whether a registry or epi-study needs consent and things like that, is always up for discussion and debate.

There are certainly privacy obligations.

But for most of our registries, through actually long discussions with OHRP, we have been persuasive in saying those are not research because they are necessary for taking care of patients and protecting them.

So, they mostly don't have those things.

DAVID FORSTER:

And I think that is great that you are certain of that.

I don't think a lot of us in the regulated community are certain of that.

MODERATOR:

David Magnus.

PRESENTER: DAVID MAGNUS

DAVID MAGNUS:

Thank you very much.

It's a pleasure to be here.

I'm really going to make three points.

I want to talk about the meaning of risk, a little bit about the nature of harms and values and then some guidance about informed consent.

So, for purposes of definition, I think it's important to be very clear about what risk means.

In the literature on scientific risk assessment, they often try to use the notion of expectation value.

But in any case what we are really interested in is the probability of a harm and its severity or magnitude.

So when we are talking about risk, that's we are really talking about.

I think we need to distinguish between different levels of risk.

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There is the harms from the clinical condition that a patient might be exposed to and the known risks of available clinical interventions, there are the risks associated with the arms of the study, which in comparative effectiveness research will often but not always be the same thing, as the SUPPORT study demonstrates.

And then there is the actual risks of research, i.e., being randomized on a protocol within the standard of care.

And I think in light of the last few speakers, I think it really is important that when we think about the risks of the research, throughout the regulations, that we use the standards of 46.111 and recognize that it really is just the latter that we are talking about as to risks of research particularly in assessing the level of risk for a study and whether it counts as minimal risk.

It's the latter that is relevant.

The difference between being in a study versus not being in a study.

So I'm going to give a simple hypothetical. I don't have time to do a detailed example. And then a couple of comments I'm going to make.

Suppose you have two interventions for the same intervention. There's no evidence to support a preference for one over the other. That is they have the same expectation value.

But suppose 75% of physicians prefer A due to exogenous factors, maybe the pharmaceutical company that produces A, spends more money than the company that makes B.

And suppose we want to do a randomized study in which half of the participants will get A and half will get B.

I'm going to claim that there is no difference in risk between enrolling in such a study and standard clinical care and hence it is minimal risk.

Obviously the product of the probability of harm and severity of harm in this particular case are equivalent whether you're in research or not.

However, even though that is true, so it is clearly minimal risk study, it is or that means several things.

Rejecting the claim that individualization and clinical judgment in the absence of knowledge is automatically less risky or of greater benefit than being on a research protocol.

There has been a lot of discussion about the fact that that is false and it seems to be clearly that existing evidence suggests it is false.

We should recognize that exogenous factors, these are again all well documented, that physician history, geography, advertising, detailing, all play a huge role in determining physician preference.

Certainly that is no better than research protocol and the evidence suggests that even when we have strong evidence about what is best, it is challenging to get physicians to change their behavior and maybe one of the reasons why patients do better in research protocols regardless of the intervention they tend to do in clinical care.

Because patients receive something different, something that has been said in debate about SUPPORT, because patients receive something different than what they would have otherwise received doesn't mean the risk is increased or benefit reduced.

It doesn't necessarily mean there's a change in the expectation value.

In this hypothetical, the probability of getting A or B is different in research than in clinical practice, that doesn't mean there is a difference or increase in risk.

The expectation value is still the same, regardless.

Now having dealt with this issue about risk, and recognizing that in general, CER will often be minimal risk, there is a different question about what we should say in informed consent.

I think it's important to understand the role of values and harms.

We are often on IRBs called on to commensurate very disparate harms in research, supposing in that hypothetical case of A and B, supposing the severity of harms are the same, they are comparable reasonably by the IRB.

But the nature of those harms are different.

If exogenous factors determine whether physicians offer one treatment or another in that example, I said an IRB might find the study to be minimal risk even if the harms are different.

So though an IRB might find the risk comparable, individuals may vary in how they evaluate the severity of different harms.

So even if they are comparable, individuals may vary how they look at that.

The more similar the risks and benefits, the more reasonable it is to consider waiving documentation of informed consent or even waiving informed consent, if the other regulatory requirements are met, the more it makes sense to attempt alternative models of informed consent, and the more it makes sense to have straightforward consent forms to explain the randomization and then allow the clinical consent to do the work of the clinical risks and benefits.

In contrast, if the harms are sufficiently different even if reasonably deemed to be comparable in severity by IRB, it is more likely the individual variation in the evaluation of the severity of the harm and as a result in cases of such variation, it's important the informed consent include differences in harms between the arms of the trial which may often in comparative effective research correspond to the different arms of the treatment options.

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Again, that is consistent with saying this is minimal risk and articulating that in the informed consent forms.

So as a result, I want to give the following guidance for IRBs.

I'm going to ask that you give this guidance.

For research within standard of care, where there is no evidence of increase in risk for being enrolled versus not enrolled in the study, finding of minimal risk and stating that in the consent forms is appropriate.

But, IRBs should assess the degree to which individual variation and assessment of the severity of harm between the arms is likely and if such variation is reasonably anticipated, informed consent forms should have a clear explanation of the difference in potential harms between the arms.

That's why in the SUPPORT study, I think it was quite appropriate to decide there shouldn't be a waiver of informed consent in that particular study and why it was important to talk about the differences in anticipation of the retinopathy of prematurity and between the two arms.

So I would ask that this be given guidance for IRBs and evaluating this area of research.

Thank you.

MODERATOR:

Excellent.

NIH.

KATHY HUDSON:

I have a question about your last point which is not up on the slide but I have it.

Where your guidance is that IRBs should assess the degree to which individual variation and assessment of the severity of harm between arms is likely.

What do you mean by individual variation assessment?

I'm not sure I understand that.

DAVID MAGNUS:

So, you are doing a trial and IRBs decide that -- let's say there was uncertainty about whether or not there was increase in death at the low ends of the oxygen level.

So there was some question, it was possible and you don't know, but we knew there was a large increase in blindness.

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You can imagine an IRB saying in those circumstances that you might be in equipoise between those two.

Uncertainty and a small difference in death, very large difference in blindness, the severity of harms in those two cases are comparable so you will judge those things as equivalent.

But individual patients or parents might say, well, I would much rather risk blindness than even a small chance of death.

And other people might say, if it's small enough, and uncertain enough, blindness is terrible and I don't want that.

So there's going to be variation.

So when you have that kind of variation in the evaluation, those shouldn't be eligible for waiver of informed consent -- period.

And it's important the differences between the two arms should be accounted for, the difference in the risks.

Even though that is normally would be covered in clinical consent, given what we know about the inadequacy of clinical informed consent, I think those should go into the informed consent forms.

In contrast, though, there is no real difference, and the only difference anticipated is we don't know which is more effective.

The harms are pretty similar.

The only thing we don't know is what the differences in efficacy is going to be, and in that situation, if it meets the other regulatory requirements for waiver of informed consent, it should be eligible for that and it means those consents probably can be restricted to simply describing the fact they will be randomized without having to explicate the differences in the risks between the two arms which would then be handled in the clinical context.

MODERATOR:

OHRP.

JERRY MENIKOFF:

So if I could pick up on what you're discussing here.

So your distinction in the last scenario is more very, very small risks in terms of things the IRB might say don't have to be used in terms of differences?

DAVID MAGNUS:

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It's not about the degree of risk.

It could be a risk of death.

But if the risk of death is equivalent, whether you're in research or in clinical practice, if there is no difference between the risk between those two, then it is appropriately seen as a minimal risk study and the two arms have no difference between them, then that would normally be covered by the clinical consent.

But if the nature of the harms are sufficiently different so that different people would reasonably have different views about that, even though IRBs might appropriately find them to be an equipoise and commensurate them that way so they find the severity the same, it could be a minimal risk study but nonetheless be critically important that the differences between those two arms be accounted for.

And I think this accounts partly for the intuitions people have about the SUPPORT study.

JERRY MENIKOFF:

Because that's what I'm trying to understand.

So on one hand you could have increased risk of going blind and the decreased risk for dying and on the other end or the flip side it, I suspect a lot of people would be troubled by the notion of concluding that is minimal risk because we are back to the usual reason for making that determination is that you are probably going to try to waive informed consent.

DAVID MAGNUS:

We find things to be minimal risk all the time without having waivers of informed consent.

JERRY MENIKOFF:

Can I ask you what the purpose is making that?

DAVID MAGNUS:

For every protocol we assess whether it is high or moderate or minimal risk.

All sorts of things could do with the nature of the review, if it's eligible in the second year for expedited review and it's appropriate even for the consent form.

I don't think it's a problem for the consent form stating very clearly there is no increase in risk as a result of doing this research versus the risk they would get otherwise in clinical care because---if that is true.

If no increase in risk, no matter how risky the two arms are, if there is no increase in risk as a result of being enrolled in the research versus being in clinical care, then there is no increase in risk for being in the research.

I think that is appropriate to state in informed consent form, even if the nature of the incommensurability of the harms means that you probably ought to make sure that the different nature of the different harms are articulated in the informed consent forms.

MODERATOR:

FDA.

ROBERT TEMPLE:

So, this is probably just my ignorance.

What difference does it make other than the possibly of waiving consent, to conclude that something is minimal risk versus slightly more?

DAVID MAGNUS:

Let me go back to what John Lantos said earlier.

It is important even in the consent forms that we be accurate in what it states about things.

Making the research sound riskier than it really is problematic and doesn't support informed decision-making.

ROBERT TEMPLE:

I agree with that.

You have to give a good description.

But the sort of rating of it as minimal or slightly more than minimal.

What difference does that make?

DAVID MAGNUS:

In practice there are a lot of things that would do in the IRB realm like I said, in terms of expedited review on its renewal, but it also means if there's a reasonable finding of minimal risk, it's appropriate for the consent documentation to state that there is no expectation of increase in risk for being enrolled in the research versus what they would otherwise get in clinical care.

I think it is important to state that very clearly even if you believe because of nature of the incommensurability of the harms that people might disagree with for the two harms, that those harms in the two arms need to be included in the informed consent form.

I think those things have not been sufficiently separated.

ROBERT TEMPLE:

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But we are mostly not talking about waiver—

DAVID MAGNUS:

No.

ROBERT TEMPLE:

The idea of waiving --

DAVID MAGNUS:

No.

The only guidance I'd recommend with regard to waiver is to claim if you have radically insurmountable harms, even if it's minimal risk, it should not be eligible for waiver of informed consent.

PRESENTER: CARL D'ANGIO

[\(Return to Agenda\)](#)

CARL D'ANGIO:

I would like to thank the department for allowing us to speak today and I need to think and acknowledge the coauthors at the University of Rochester who helped to put this together.

I'm going to start by stating we agree that informing and protecting subjects is of paramount importance in what we do.

And the goal of our comments is to improve the informed consent process and research as well.

I'd also like to thank the panel for their careful reading of the written comments people have submitted including ours.

Our written comments covered the various types of risk and a hierarchy of risk that others discussed in some detail and I won't talk about -- We touched on the counter productivity and complex consent forms and argued for trying to find better ways to inform people of what they are getting into in research.

And we also talked a bit about the inverse nature of risks and benefits in comparative effectiveness research, which makes expressing those potentially different in comparative effectiveness studies.

What I'd like to spend time on is the risks of randomization itself and how to try to understand that.

I'll admit I'm going to use short hand of comparative effectiveness research being equal to research that compared interventions within the standard of care and I recognize that glosses over many linguistic and ethical and scientific details that I'd happy to talk to someone about later.

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What I'd like to introduce is the concept of transactional risk which is putting a name on something that many other people have commented on. And that is the variation and treatment for reasons that are extrinsic to the patient that occurs in the course of routine clinical care.

That could be due to differences in resources, differences in physician preferences, and differences in drug detailing, and differences in education that people have already mentioned.

As a result, two similarly situated patients could receive different therapies for the same condition.

That difference in the application of therapy would be nonsystematic.

I won't call it random, but somebody might.

And it is not related to the patient characteristics. If it is related to the patient characteristics, it is outside of this discussion.

Randomization itself is a method of allocating subjects in an unbiased manner.

Randomization is a discrete activity and therefore doesn't itself introduce risk, but the result of randomization can introduce risk. And we agree with others that randomizing someone into the study is different than having their own physician treat them although the outcome may not be much different than having their own physician treat them.

In comparative effectiveness research, we argue research risk is the difference between the transactional risk experienced in routine medical care and the risk of being randomized as part of this study.

That's different from classic experimental studies where it's very easy to figure out what the baseline is and what the increase is.

Here the baseline, we argue, is the transactional risk of receiving care for the illness or the disorder the patient is already suffers.

So in comparative effectiveness research randomization and comparing effectiveness – randomization systematizes, but doesn't alter the transactional risk of standard care.

The difference in risk conferred by randomizations may in some cases be considered minimal.

The situations in which the risks of randomization might be considered minimal would include the studies comparing standard of care treatment options that are available within the community, and definition of community is one that we have to be clear on.

For subjects participating in the study, the standard of care options would be available under the normal course of receiving medical care and the studies would be eligible in the course of clinical care for either treatment option.

Someone who is not eligible for other treatment option does not belong in this study deserves to be treated with the treatment option that is better for themselves but as I have heard many people say today, we call it research because we don't know yet.

Applying the standard of difference from transactional risk would have little practical effect, in most cases, among interventions applied on individual basis; for instance, getting most medications, receiving most surgeries, respect for persons would dictate that individual consent, that individual consent be obtained, including the description of the options.

The way many have said we should be describing to our patients anyhow.

The difference and where I will rush in where Dr. Annas dared not tread this morning, is in cluster randomized trials.

In cluster randomized trials, centers rather than individuals are assigned to interventions and in that case, a waiver of consent may be permissible either pre-randomization or post randomization. If a standard of care waiver consent might be reasonable, if a standard of care treatment, for instance environmental approach across the center to prevent falls is randomized and delivered on the center-wide basis, if the difference from transaction risk is minimal, if it's possible that somebody could be admitted to hospital where this environmental approach is in place versus one that isn't, if the individual delivery of the intervention is not possible, it is an environmental control that can't be altered from patient to patient; consent would be impractical --impracticable, that's a real regulatory word in this setting. And waiver of consent in that case might be a reasonable option.

That doesn't mean that subjects should not be informed but information should be provided by an alternate means.

With that, I'll thank you.

MODERATOR:

Excellent.

Thank you.

I'll start with FDA.

ROBERT TEMPLE:

You go first.

MODERATOR:

OHRP.

JERRY MENIKOFF:

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I'd like to thank you.

I particularly like your separation of the cluster trials versus the other ones.

These are among the complicated issues many, many people are dealing with including on the governmental side and this is very helpful, thank you.

MODERATOR:

NIH.

KATHY HUDSON:

I also appreciated your comments about cluster randomization and talking about waiver of consent may be permissible.

And certainly the, sort of just the time, energy, cost involved in going through individual informed, consent, not just the form but the whole conversation about that may be a disincentive to informed consent in the cluster randomization study.

But I'm wondering, isn't there something short of consent that we could encourage as a notification that this research facility is participating in a trial in order to improve blah, blah, blah?

And therefore, at this facility, if you get dialysis, you will get – the whole sort of notion of an informed participant community rather than that hospital was doing this and we didn't even know about it.

CARL D'ANGIO

We would agree with that, absolutely that transparency is important.

People need to understand what is going on.

What would be a false choice for patients in that institution and therefore subject to study, would be to say, and you have a choice.

No, the rails are already up in that bathroom.

We are not getting to have somebody come in and take them down.

Now granted, most places should have rails.

Sorry for the silly example.

But that does not mean that people shouldn't know that this is going on.

It's more a matter of whether it is practical and possible to decide to be in or out.

MODERATOR:

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Thank you.

FDA.

ROBERT TEMPLE:

Only to say the comments on cluster ram randomization is help.

We are all collectively actively thinking about that, as you can obviously tell.

Thank you.

MODERATOR:

Thank you.

PRESENTER: JON TYSON

[\(Return to Agenda\)](#)

JON TYSON: Thank you.

I want to -- I speak on behalf of my colleagues today as an epidemiologist, a neonatologist, a co-investigator in the SUPPORT trial, and like all of us in this room, a past and future patient who hopes that when I get sick, there will be proven effective therapies.

I have prepared slides today to try to provide generic answers to the questions posed by OHRP.

But I can't escape feeling that I should offer some specific comments about the SUPPORT trial.

First is, based on the best available evidence, the investigators in that trial did not believe that mortality would be increased with reduced or lower saturation levels.

There was considerable concern that oxidative stress, pulmonary insults from high oxygen exposure would increase mortality in the higher saturation goal group.

As you may know, the belief that 100% oxygen was a good thing to use in resuscitation of high-risk babies, appears to have increased mortality over the years simply because of the supposition that more oxygen is necessarily good and life-saving.

In my own clinical practice, at the time I was using 85-89 as my goal because that was my best guess as to what would produce the best outcomes: the lowest ROP without an increase in deaths.

I guess it looks like I guessed right on one outcome and wrong on the other.

But, I believed that we should do a trial so that neither I or all the other neonatologists in the world would have to keep guessing about this.

Second point is, that there is no evidence that the babies in that trial had a worse risk adjusted outcome than other similar babies not enrolled.

And third is, I'd ask to you recall that the IRB Guidebook defines experimentation as the use of unproven therapies whether or not research is being performed.

So babies, whether they were in this trial or not, whichever oxygen saturation goal their physician selected, were experimental subjects whether or not they were research subjects.

So, for this question, the second question posed by the IRB, I think there are at least three important issues.

First is, this should be based on the best available evidence of reasonably foreseeable risks, including plausible but poorly studied hazards, and hazards found in the systematic review of trials, or in the absence of such a review, in one or more trials or well-performed cohort studies at a significant or marginally significant level.

Investigators shouldn't be required to list all others.

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They may well indeed distract from the hazards that are more likely or more important to patients.

Secondary outcomes aren't necessarily reasonably foreseeable hazards.

So investigators often have an exhaustive list of all potentially important outcomes to be sure that we are carefully monitoring those, and that if there are unexpected findings, that they will be accepted as pre-specified by reviewers and journal editors.

The issue of death as a competing outcome, I think it's caused a lot of confusion.

As in SUPPORT, trials in lots of high-risk patients, patients often die without having the quote, "opportunity to experience the adverse outcome that the treatment is hypothesized to reduce."

And even when there is no hypothesized or plausible effect of that treatment on death, it is appropriate, often desirable, to have a primary composite outcome that includes death, for example, death or myocardial infarction.

So, the reasons for this include first, excluding any patients, particularly deaths, after randomization in a comparative effectiveness trial; may cause baseline differences between the groups that before they were excluded they were similar; violates the intention to treat principle for analysis of clinical trials in general; and may confound the results and produce misleading and inaccurate conclusions.

The inclusion of death in the primary outcome is particularly a good thing to do, to have done, if for example, you get unexpected results.

There was a trial, for example, of intensive glucose lowering that reduced myocardial infarction has hypothesized.

But to the surprise of the investigators, increased death.

You want your primary outcome to be compatible with your conclusions.

In this case, that wouldn't have been the case.

Third is, the need to improve risk disclosure for unproven therapies exist in clinical practice and in clinical research.

We need a lot of studies about the wants and needs and comprehension of patients for emergency therapies as well as non-emergency therapies.

We've heard a lot of conjecture today by people who are not representing patient views directly.

And we need to know more about the factors that affect the validity of consent and about the effects of risk disclosure.

There may be adverse effects as well as beneficial ones.

The different risk disclosure -- systematically different risk disclosure -- for the same unproven therapy in comparative effectiveness studies and in clinical practice, I find very hard to justify based on any ethical principle that anyone in this room would espouse or any survey of well-informed patients.

Question three...

MODERATOR:

Your seven minutes are up.

JON TYSON:

Should randomization be considered to present a risk to subjects?

No, not in legitimate comparative effectiveness trials, and I think I'll just stop at this point.

MODERATOR:

Thank you. Let me turn to the panel. FDA?

ROBERT TEMPLE:

I have just forgotten my question.

Come back to me.

MODERATOR:

NIH?

KATHY HUDSON:

Thank you very much for your presentation.

I especially appreciate your comments and explanation of death as a competing outcome.

It has been a particularly confusing element to the discussion about the SUPPORT trial and I admit not being a clinical trialist by training, that it took several goes at it before I completely understood how it was incorporated into the SUPPORT study.

I appreciate your presentation of it today.

I wanted to just make a comment about your suggestion that additional studies are needed to really examine how do patients and prospective subjects view all of what we have been talking about today.

And the NIH will be shortly awarding a number of grant supplements to look at exactly this issue because we do need their perspective to guide us as we move forward.

MODERATOR:

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FDA?

ROBERT TEMPLE:

I remember now.

This is about the SUPPORT study and whether anybody even worried even a little bit the lower oxygen levels would have a bad effect on outcome.

I guess it's always been hard for me to understand how knowing that higher oxygen improves survival and the desire to lower oxygen levels to improve ocular outcome, wouldn't at least create some concern that you might have gone too low?

I mean, everything has a dose-response.

The increase in oxygen that leads to improved survival must have a dose-response curve.

It must. Everything does.

Why would there be no worry that going lower wouldn't do harm?

JON TYSON:

We were using data from recent studies, not data from studies in the '50s, in which many of these studies quoted, babies were not given more than 50% oxygen even if they were blue and gasping and dying.

That is very different than measuring oxygen saturation.

And as best we could tell, this was of a safe range.

We were in equipoise about whether one group would have a higher mortality than the other.

There was an observational study by Tan et al who reported that saturations as low as 70 were safe.

And I would also say that it is not a given that a goal of 85-89 increases mortality.

If we had better technology to adjust the FIO₂ to the baby's needs, and perhaps even if we had better staffing in our nurseries, so there could be a quicker response and finer tuning of that, to prevent those very low saturation levels.

ROBERT TEMPLE:

I would never have said it was a "given."

Obviously we wouldn't have done a trial if it was a given.

But, you said you were in equipoise about it.

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If you're in equipoise about it, that means that there is a possibility that it could be worse.

And then the question arises, don't you need to tell people?

JON TYSON:

So my proposal is, you base it on the best available evidence.

Based on the best available evidence, we didn't think the lower saturation goal would increase mortality.

ROBERT TEMPLE:

No, well, I mean, we'll probably go at this more.

I understand you didn't think it would.

You probably wouldn't have done the study if you thought it would, if there was real evidence.

But that there was a concern...

JON TYSON:

We thought the difference would be in eye disease.

ROBERT TEMPLE:

I know.

But, given -- it's a little hard to accept the idea that there wasn't any concern that it might go the other way....

JON TYSON:

If we had found the opposite result, you would be sitting here saying, gee, What about these studies that reported more bronchial-pulmonary dysplasia?

What about these studies in resuscitating asphixiated infants?

Where we now have a meta-analysis saying 100% oxygen increases mortality.

MODERATOR:

I'm going to stop you.

ROBERT TEMPLE:

OK, just one last one.

What I'm really saying is that in the areas of uncertainty, maybe patients, some explication of what the uncertainties are?

MODERATOR:

OHRP? Did I give you a chance?

JERRY MENIKOFF:

Thank you for the helpful comments.

MODERATOR:

Thank you.

PRESENTER: MICHELE WALSH

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MODERATOR:

Michelle Walsh

MICHELLE WALSH:

Thank you for allowing me to present today. Traditional research is the context in where the common rule was promulgated where there is a control group, which receives the standard or in legal ease, standard of care, or experimental group with new or untested treatment.

However, this traditional paradigm doesn't recognize there may not be one standard but many standards. For example, there are currently over 100 drugs licensed for hypertension by the FDA and each of these is a standard. Comparative effectiveness research as has been promoted defined by the patient centered outcomes research institute as evidence designed to inform health care decisions by providing evidence on effectiveness, benefits and harms of approved treatments.

There is by definition no experimental group that is a group receiving a new or untested treatment. PCORI, recently promulgated detailed guidance on the methods to be used in comparative effectiveness research but these extensive standards are silent on the approach to informed consent in these studies.

I think everyone here have agreed and many have said, that we recognize that consent is a process, not a form. Despite ever longer consent forms, comprehension of studies is imperfect. There are a number of studies that have explored this, Sanchinie and colleagues assessed the effectiveness of the consent process in a well-regarded adult study randomized trial of two different cancer treatments. Within the months after enrollment and accessing participants understanding, 62% understood the purpose of the study; 44% understood the study procedures; but only 40% could correctly list at least one major risk. Indeed, OHRP has recognized that in effective informed consent is a process, not a form. However, it is obvious that existing informed consent processes can be improved. Many studies have been published as investigators have recognized the need to improve and this systematic review demonstrates that

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enhanced discussion an improved consent form show the most promise for improving the consent process.

Unfortunately, the use of multimedia techniques or graphic displays to demonstrate risk or benefit didn't result in improved understanding. Let's jump to a hypothetical case. A competent adult patient undergoing major surgery has postoperative pain medication selected by the individual treating physician, morphine or fentanyl. There's limited evidence of the superiority of either drug however there is a four-fold difference in price.

Let's walk through this and different study types to demonstrate an ethical framework. As has been highlighted here many times today, routine medical care does not necessarily fully inform the patient where the choice of the individual physician may be less about the individual patient characteristics but rather about physician preference often by how they were trained, institutional habits or pharmaceutical detailing.

If instead the patient is asked to participate in a observational study where the treating physician again chooses the pain medication, there is improved disclosure of both benefits and risks associated with those routine treatments.

If instead, this is the traditional randomized clinical trial, again, the ethical framework is fully met. Randomization does not change the risk of either treatment. Participants are carefully monitored and the protocol provides distinct exit criteria if pain is not adequately controlled or complication occurs.

Within the context of the trial, care is individualized by the treating physician not the investigator. Now what if this is a prospective comparative effectiveness trial? The treating physician chooses which drug is assigned, consent is given, data is collected to fully assess the risks and benefits. I would argue that there is no compelling evidence than informed consent in prospective CER of this type should be handled differently than any other research, especially in the interest of transparency.

However, comparative effectiveness research, effectively lives at the interface between randomized control trials and other newer forms of research called quality improvement learning networks, yet patients, even in QI learning networks, can be fully protected by the routine provision of information that the hospital where the patient resides routinely seeks to improve care through continuous improvement methods. As required by the joint commission on hospital accreditation. Indeed, if we look that from a justice standpoint, what patient would want to seek care in an institution that did not seek to continually improve. So we are going to get informed consent for this hypothetical case. What might the consent form look like?

The benefit is clear. Alleviating postoperative pain but what potential harm should be disclosed? The risks here are taken from the drug insert for morphine in the PDR.

There are additional 22 lines that will not fit on the slide. However, if instead the consent form presented risks in a tabular form graded by how frequently potential harms might occur, understanding would be greatly improved.

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Multicenter trials have become the strongest method to evaluate new treatments or to evaluate existing but unsteady treatments and they do represent special challenges in informed consent. Respect for persons requires that information on benefits and risks disclosed to participants should be identical between sites.

Yet individual IRBs exercising their local control frequently alter model consent forms.

Use of a federated IRB mechanisms should be encouraged for multicenter trials. In addition, reasonable readability standards, I would suggest, eighth grade level, should be promulgated and enforced by the OHRP.

Finally we need guidance on recommendations for informed consent as we hurdle headlong into the electronic medical record era.

In conclusion

MODERATOR: Your seven minutes are up.

MICHELE WALSH: Thank you.

The common federal rule has protected research participants and guided investigators well over the last decade. Newer research methods can be addressed within the current framework.

Thank you.

MODERATOR:

Thank you, let me turn first to NIH.

KATHY HUDSON:

Thank you very much.

I had a question and maybe I was spacing out for a second. In your discussion about quality improvement, I agree that certainly patients in health care systems are interested in improving quality, but in terms from a patient's perspective, or participant's perspective, what's the difference between some, if you looked at something that was quality improvement and it was not labeled as quality improvement, could you tell the difference between quality improvement and comparative effectiveness and how the difference in terms of transparency, consent and those two areas.

What are your thoughts on that?

MICHELE WALSH: I think you have identified it completely well that there is no difference in my way of thinking. And I think that participants are best served through an informed consent process. At a minimum, a letter of information notifying them that this is going on. In our own context of the statewide collaborative, we had IRB approval for every QI intervention.

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KATHY HUDSON:

Thank you.

MODERATOR:

OHRP?

JERRY MENIKOFF:

Thank you for the helpful comments. We were talking about what comparative effectiveness research was in your early slides and you noted there is no experimental group. I'm just wondering your take on some of the earlier comments we got in terms of some of these studies for example where there is a continuum of treatment and we are not sure exactly what criteria physicians are using in terms of plopping and assigning you to a particular value. It sounds as if there might be some studies in which its unclear if experimental is the right word, perhaps not. But there is some notion of perhaps risks related to these trials yet on the other hand fully acknowledging there are other studies where it is much clearer to say there is nothing experimental. Do you agree there might be such lines?

MICHELE WALSH:

Yes. I agree there is such a line.

MODERATOR:

Thank you. FDA?

ROBERT TEMPLE:

We are aware of one study of two widely available drugs that used online informed consent that was very interactive, people asked questions; if they didn't get it right, they had to do it again. For comparative effectiveness or things where the drugs involved are not very familiar where it shouldn't be that complicated, does that seem like a promising avenue? Current informed consent forms are too dense far too often.

MICHELE WALSH:

I completely agree with you that current consent forms are very similar to the FDA product insert in many ways. They are very similar to the FDA product inserts in many ways.

[Laughs]

ROBERT TEMPLE:

Those are directed at the most knowledgeable people in the world.

MICHELE WALSH:

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They have complete information but perhaps not presented in a way that makes it very informative for the participant. I was very disappointed in the systematic review I cited in that I personally hoped that some of the more interactive multimedia studies would give us a way out to try and be sure that our participants are more fully understand what it is they are agreeing to. That said, at my own institution, we had pushback from our IRBs when we had parental agreement to participate in a study and yet, we concluded at the end of that process, that they didn't really understand what they had agreed to.

And we went to the IRB and said, we don't think we can take this consent. We don't think it is truly informed. We were told that would be paternalistic of us to reject their right they had agreed to be in this study. So it is really a conundrum for us every day.

MODERATOR:

I'm going to once again take the moderator's prerogative recognizing the panelists have been terrific.

I know we have seven more speakers. The afternoon lull, the post lull, I've seen a few people maybe not nod but thinking perhaps with their heads down, let's take a -- let me once again punish you all and ask for a seven minute break.

We will start promptly as close to 2:30 as we can. Restrooms over there. If you need them, if you don't, feel free to just get up and stretch a little bit. We have about two more hours of timed work to do here.

Thank you.

MODERATOR:

We looked at several different models.

You all know that we did publish a second Federal Register notice stating we might cluster or order the presentations, you know look at some models for arranging the schedule.

We looked at half a dozen, four to six models or something, and our eyes were just glazed over, and we are like, you know what, let's just do it the way folks signed up.

So you're presenting in the order in which you signed up.

So you know that's how that happened.

I think it's worked fairly well.

I think there's been a lot of natural flow to the meeting that we could not have arranged better had we tried to force into either the questions we put out there or the other models that we looked at.

So we thank you all very much for your patience with the process and for your efforts

today to make this meeting a success.

So I just note for the record that we are significantly ahead but we are going to proceed.

It may affect some of our later afternoon speakers who were

planning to be here, but with logistics today, it may change everything anyway.

So without further ado, I see we have our next speakers with us, Shawn Pratt and his family are here to make a presentation.

Thank you.

PRESENTER: SHAWN PRATT

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SHAWN PRATT:

Thank you, ma'am. My name is Shawn Pratt. I'm here with my wife, Carrie, and our daughter, Dagen.

We are representing Dagen today.

I'd like to start off by saying that Dagen is a child and at the time of the SUPPORT study, a very vulnerable child, in a very vulnerable state.

She is a child, not an experiment and not a subject in an experiment, and she deserves the best possible care regardless of what type of study she may have been on.

I do have a brief statement I'd like to read as well.

Thank you for inviting us to this forum.

We as parents of a SUPPORT participant appreciate your willingness to hear us.

And our very personal comments regarding what we learned and experienced throughout our daughter's four month residence in the NICU.

We are here to introduce our Daughter, Dagen, which I just did, and share with you what we experienced with regards to the study, the SUPPORT study.

Dagen was born six years ago. She was delivered via emergency C-section at a very premature 25 weeks gestation.

From Dagen's first breath, she has been fighting and working hard to achieve every developmental milestone.

In the beginning, when Dagan was a mere one pound, 11-ounces – and she did dip down to one pound, one ounce -- we were approached by the medical staff at our hospital with the request to be participants in various research studies.

As educated professionals we understand the importance of conducting research and conducting studies, and the importance of the results of those studies on future children and the future of medicine.

Many of the studies we participated in were not invasive in nature, to include searches through meta-data contained within Dagan's medical records.

Others were relatively innocuous, such as studying the characteristics of Dagan's cord blood.

My wife, Carrie, even took part in a study on the mental effects of having a child in the NICU.

Yes, there are mental effects of having a child in the NICU.

As parents of a premature infant, we thoroughly evaluated the details of each research project before providing our consent and subjecting our medically fragile daughter to testing, testing of any kind.

We actually declined to participate in one study related to acid reflux due to certain inherent risks that we believed to be troubling, based on the details provided.

So we didn't just take part in every study that came our way.

Then there was the DHHS-sponsored SUPPORT study.

After surviving over four months in the NICU, to include laser eye surgery to correct ROP-plus disease at a mere two months old, Dagan was eventually released into our care with an apnea monitor.

Five and a half weeks following her discharge, Dagan was admitted into the PICU for failure to thrive.

As a result of severe reflux, she had Nissen surgery and a gastrostomy – G-tube inserted.

At the age of two, she faced a diagnosis of cerebral palsy.

Dagan is now a very happy child who thoroughly enjoys life despite her limitations.

Imagine our surprise, just a few months ago as we learned about the risks associated with the SUPPORT study.

Based on new information, it appears that Dagan was placed into a random oxygen saturation category, instead of a study to monitor her natural oxygen saturation.

A random category which may have led to ROP-plus disease, among other items.

A risk that may have yielded cerebral palsy which causes her to struggle daily with motor tasks, causes her to wear orthotics on both legs, and causes us to travel quite a long-distance to weekly physical and occupational therapy, and now at the age of six is causing her to present identity issues.

A risk that caused her pain as she was aggressively moved back and forth from the ventilator to CPAP to nasal cannula within four months.

Dagan experienced a multitude of health emergencies while in the NICU to include metabolic acidosis, sepsis, apnea, and collapsed lungs, multiple times of each.

The SUPPORT study looked good on paper, it looked good to us.

We provided the NICU staff with authorization to record Dagan's oxygen saturation measurements so the results could provide medical professionals with information to accurately study and hopefully reduce the incidence of ROP plus disease in premature infants.

We were led to believe that we would be helping other babies by doing the study.

That this information would be useful to help catch ROP plus disease early.

We were guaranteed that the study wouldn't hurt Dagan in any way, that it was just gathering information.

While we appreciated the need to help other babies born with problems such as Dagan's, our sole motivation was her health.

We assumed her doctors felt the same, and were shocked to learn the care she received was based not on what she needed but on some protocol.

In our minds the SUPPORT study turned Dagan into a subject of an experiment, instead of a participant in a study.

We want to understand why the intent of the study was not originally provided to us as it was envisioned by its designers.

We want to know as information comes in, why the risks and intent of the study were not clear.

If it were clear, we wouldn't have taken part in the study.

Why was our child a subject in a medical experiment without our knowledge or permission?

What information was eventually extrapolated from the experiment?

How did the information help other babies?

Did the study catch ROP plus disease early in other infants?

Tell me that the SUPPORT study did not hurt Dagan any way.

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I'd like to know that information.

Finally, I need to ask you, would you place your own medically fragile premature child into the SUPPORT study?

Thank you.

MODERATOR:

Thank you.

Questions from the panel?

I'll start with NIH.

KATHY HUDSON:

Thank you very much for taking the time to share with us your comments and your story, which has been a challenging one and our hearts go out to you.

I wanted to just reassure you that your comments are really going to help us as we move towards improving the research ethics that we take very, very seriously, and we really appreciate your comments and your input today.

Thank you.

SHAWN PRATT:

Thank you for having us here, ma'am.

MODERATOR:

Thank you. OHRP?

JERRY MENIKOFF:

I'd like to echo Dr. Hudson's comments, and particularly on our end on behalf of OHRP.

Ultimately, it's about giving appropriate information to subjects, in this case, parents, and the one thing you really want to know is what do parents actually understand.

So your taking time and effort to come here, we so rarely get this exact type of information.

So thank you so much.

SHAWN PRATT:

Thank you as well, sir.

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MODERATOR:

FDA?

ROBERT TEMPLE:

Just to be sure I understood, you got some kind of consent form, but I take it you're saying that you couldn't tell from that, that there were actually two things that she was going to be randomized to?

One the oxygen level and one the nature of the pulmonary support.

But that wasn't clear?

Is that what you're saying?

CARRIE PRATT:

When they told us about the study, they said, they are collecting data, that don't worry, she is going to be cared for.

Like, now we are realizing that we didn't understand what was going on, and we realize that risks weren't put out.

But with that said, even approaching us at such an incredibly stressful time, I mean, I think of, there is a cooling-off period to buy a car.

Like we are talking about our child.

So no, I can't say that from what we've heard today and what we've read, that it makes sense to our experience.

ROBERT TEMPLE:

So they didn't really communicate that it was in fact an experiment?

It was an experiment.

There were two different...

CARRIE PRATT:

No.

ROBERT TEMPLE:

...It was complicated.

CARRIE PRATT:

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So if we would have known that, we would not.

I mean, as he said, there was an experiment on reflux, and we knew she had reflux.

And there were so many risks on there, and we are like, we've got to say 'no.'

And then work -- because she's an individual.

We have to work with her medical team to find out how to fix this.

And yes, she went home and then we had to go back for the Nissen and the G-tube. But if the risks were written, then we would have felt informed.

But they weren't.

ROBERT TEMPLE:

And we wouldn't be here either.

SHAWN PRATT:

Thank you, sir.

MODERATOR:

Thank you.

PRESENTER: SHARISSA COOK

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SHARISSA COOK:

My name is Sharissa Cook and my son's name is DRAYSHAN Collins.

He was born at 25 weeks and weighed one pound, 11-ounces.

Within the first three days after birth he went down to one pound, seven ounces.

I will be addressing questions number two, number three and number five.

Health care professionals know what constitutes an oxygen level that is too high or too low.

They are also aware of the health ramifications of an oxygen level that may be too high or too low.

Therefore, I believe that they should have conveyed to me the effects of my son's oxygen levels being too high or too low.

That information should have been given to me at the time I was asked to put him in the study.

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Had I known the full extent of the study, I would not have given my consent.

The medical personnel who approached me were not forthcoming with the information in their possession, therefore, taking away my ability to truly make an informed decision.

However, due to the lack of information provided regarding the potential risks involved, I unknowingly place my son in harm's way.

I trusted them with my baby's life.

First the IRB should be aware that women who have just given birth to a premature baby with serious difficulties is in a very vulnerable state.

The only thing that mother wants is for her baby to be well and she will trust the doctors have that same interest at heart.

And in that state, we are not thinking about medical research or what is good for some baby in the future.

Only what is best for my baby now.

The name of this study was SUPPORT.

That name alone is an inducement to participate.

What mother would not want support?

It implies only good, only help, no risk.

I believe that the randomization process should be fully disclosed.

No matter which group you're placed in, the consenting adult should be fully informed of the risks that are associated with each group prior to giving consent.

If you do not present the risks associated with participation in a study, you take away my ability to make an informed decision.

The known standards of care should be fully explained to potential participants.

Additionally, the information should be presented in such a way that a person with any level of education can understand what is being asked and any potential ramifications associated with participation, regardless of the group assignment.

Informed consent should not be waived at any time.

I do not understand how anyone can ask in good conscience, someone to participate in a program that may be detrimental to their loved one's life when they are aware of the potential risks involved.

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In a study they involves human life, any potential risks should qualify as a foreseeable risk.

If there is documented belief in a medical community that an intervention within the standard of care increases the risk of harm, that information alone should be enough to cause trial facilitators to tread with caution and take care to make certain that participants are informed regarding information that is already available.

In closing, my son is alive, breathing human being.

He is not simply a subject.

I feel there was a lack of information given to parents, and because of this, I feel taken advantage of and I feel responsible for my child's participation in this study.

This is difficult to comprehend.

I truly wish I was given all the details of the study and that Federal guidelines and regulations would have been implemented and followed.

I feel that doctors should have explained to me and told me the difference between the guesses they would make outside of the study versus inside the study.

I wondered if the guess would have been different.

Thank you.

MODERATOR:

Thank you.

And we will try to get those slides in to what we post as the archive for the meeting so it is there, your presentation.

Let me first go to OHRP.

JERRY MENIKOFF:

I don't have any questions but I want to thank you very much for coming and again rest assured that hearing this set of information from parents like yourself is crucially important.

And we will take account of it as we move forward.

Thank you very much.

MODERATOR:

FDA?

ROBERT TEMPLE:

Were you clear on the fact that this was in fact an experiment?

That it was comparing two things?

That people were going to be randomly assigned?

That was part clear?

SHARISSA COOK:

No sir, I was under the impression this was more of a support group, I guess I should say, where they would be holding our hand throughout the process to let us know if there were any type of delays or anything that we could do since they were premature babies. You know, it was my first child.

So I was under the impression that this was more of more support and this is something that would be beneficial to me as well as my son, because we have someone there to help us along the way.

ROBERT TEMPLE: That certainly isn't what the trial was about.

Okay, thanks.

PRESENTER: EDWARD CAMPION

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EDWARD CAMPION: I'm Edward Campion.

I'm an internist and geriatrician.

I'm also senior deputy editor of the New England Journal of Medicine and a member of the staff at Massachusetts general hospital.

But I speak as an individual.

One of the pressing needs in medicine today is for rigorous clinical effectiveness research.

This means research on interventions that are within the currently accepted standard of care.

Most decisions that physicians make are not based on evidence from randomized control trials or from other rigorous research.

From clinic to the ICU, most of what is done every day relies upon a combination of a physician's personal experience, what he or she has been taught by others and an understanding of disease processes as well as upon local standards and expert recommendations.

We also know that usual medical care varies widely depending on where a patient is, what may be standard practice in Miami is not seen as standard in Minneapolis.

Usual care in Seattle may differ from usual care in San Antonio.

This applies particularly to uses of technology and high-cost interventions.

Too often we don't really know which approach produces the best outcomes for patients.

Making progress depends upon research on the various options within the usual standard.

Often, this means comparing often this means comparing an expensive newer intervention that may be seen as an exciting advance with an intervention that has been around for many years.

People may feel one intervention is superior but that view is not based on firm evidence.

In accessing standard of care research, the crucial first test for an IRB is to establish that the interventions being studied are in fact entirely within the current standard of care.

That can be established from the evidence that the interventions in question are being used in a way similar to that in the proposed research.

Standard of care status can also be established from relevant professional guidelines, textbooks, point of care tools, articles in the peer review literature.

Once it's established that the interventions are recommended and in clinical use, then randomization between them does not pose any additional risk.

In such situations, the research itself poses no additional risk.

Depending on the severity of the disease and the interventions, there may be substantial and foreseeable risks to the patients but those risks do not derive from the randomization between different treatments that the medical profession sees as reasonable alternatives within the current standard of care.

What do patients need to know?

First, if a patient is assigned to an intervention randomly, then the patient needs to know that and he or she needs to approve of being in the research trial.

Anything else risks the essential trust and understanding of our patients.

However, patients should be able to agree to participate in a trial by speaking with a physician, reviewing the alternative interventions and having their questions answered.

Patients can also benefit from educational booklets or videos about their conditions and interventions and research and provisions must be made to answer any ongoing questions that may arise during the trial.

Once patients agree, understand and agree to participate in standard of care research, they should be able to sign a simple consented form that is clear, short and easily understood.

Research that is genuinely within the standard of care should not be required to portray the risk of alternative interventions as risks of the research.

Those risks are inherent in the patient's condition or to the imperfect and understudied interventions that constitutes the standard of care.

It is misleading to patients, as well as harmful to clinical progress, to describe the risks as deriving in some way from the search itself.

For standard of care research, long consent forms that catalogue foreseeable risks do not help patients.

In fact, they misleadingly communicate that the research is risky.

The real risks come with the patient's condition and from the lack of evidence for many of the interventions that are in everyday use.

And the risks to the patients are only made worse by the uncertainties that derive from insufficient research within the standard of care.

I might add that I think what we are hearing most strongly today and most poignantly, particularly from the parents, is about the need for better communication, education and transparency, and that is not accomplished by the consent form.

Seven page single spaced consent form in the SUPPORT trial.

Whether an extra paragraph in that consent form would have created one iota more of patient understanding is problematic.

And the fight over what is in the consent form is so far removed from the realities of patient education and communication that it is kind of sad.

We are missing something.

And what we are missing is being square with the patients, communicating, educating, follow-up and finding ways to do that.

One the parents also said very directly and poignantly, we needed something, we needed to see something, to have something.

Not under ten or 15 or 20 page consent form, but something they can understand, take home, and learn about the trial and receive the message that transparency in a way they can understand, is part of the research.

Thank you.

MODERATOR: Thank you.

Let me turn to OHRP.

JERRY MENIKOFF: Thank you, very much.

I'm fully onboard in terms of the notion of making consent shorter, understandable, and ultimately absolutely right in terms of the patient should understand this and part of a process.

But, in terms of what they should understand, I guess I'm not sure I'm fully understanding.

Take SUPPORT, for example.

Is your ultimate position that all they have to know is that they are getting things that are part of standard of care as opposed to, I would think a lot of people would have thought there was a debate about perhaps increased risks of whatever, going blind on the high oxygen, perhaps brain damage on the low oxygen end.

Wouldn't a lot of parents wanting to know that information perhaps would have used it to decide whether or not they wanted to be in the study and therefore isn't it appropriate that they get that in terms of fully having ethically obtained their consent so they are okay with being in the study?

EDWARD CAMPION: I have perhaps I didn't make myself clear.

Patients need to understand that they are in the study, that there is random assignment, what the risks are in the condition and the treatment and that is not going to be achieved by long consent forms.

It's got to be achieved by another process, I think written materials, that are geared to the patient's reading level and for patients are under recognized and undervalued as a means for education and continuing education, particularly for people who are under great stress.

And of course those things should be -- that's the core of what it is all about.

JERRY MENIKOFF: I think we are agreeing on all this stuff here.

Thank you.

KATHY HUDSON: No questions.

ROBERT TEMPLE: No questions.

Thank you.

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PRESENTER: MICHAEL MCGINNIS

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MICHAEL MCGINNIS:

Thank you very much.

As was noted, my name is Michael McGinnis, senior scholar at the Institute of Medicine at the National Academies.

Today's discussion is of considerable importance to the vision and promise of continuous learning and health care.

And I commend The Department of Health and Human Services for conduct and for the serious attention it is giving to this fundamentally important issue.

It is important to emphasize that my statement is individual in nature.

It is essentially descriptive and personal and is not a statement or a position of the Institute of Medicine or the National Academies.

My three points are fairly straightforward.

First, there have been impressive development in the prospects and tools for continuous learning and health care and the Institute of Medicine is devoting considerable emphasis to fostering progress in that respect.

Second, systematic capture of the results from standard of care interventions is a conceptual and practical linchpin for continuous learning and improvement, and third, regulatory and cultural transformations are among the core preconditions to realizing the benefits of knowledge, generation and care improvement as natural outgrowths of the care process.

I believe many of you are aware of IOM's longstanding interest in leadership in the safeguards for individuals participating in research studies.

That commitment is unwavering.

On the other hand, with increasing frequency, as in the 2009 report Beyond the HIPPA Privacy Rules, IOM committees have also urged attention to the potential of regulatory impediments often unintended to inhibit unnecessarily the development of new insights from standard care process system ,and they highlighted the importance of practical adjustment to emerging opportunities for learning from and improving the safety and effectiveness of routine care.

Hence the three points.

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The context for the first point, the prospects in the need for continuous learning in health care is clear, compelling and well described in the Best Care at Lower Cost IOM report, the report released last year by the IOM committee on Continuing Learning Health Care in America.

Motivated by both challenge and opportunity, the report summarized what has been learned about the implications of rapid increases in the complexity of care, the persistent harm and short falls in the quality of care, and the 30% of spending on care that constitutes little more than wasted resources.

These are serious problems for individuals and for the nation and they compel us to do things in a very different way.

But as the report also goes on to point out, advances in information technology, and research methods now offer the prospect for substantial enhancement in our capacity for continuous learning and improvement.

We, in the IOM, have been working with colleagues throughout the field to map the strategies for progress towards the vision of continuous learning health system, in which signs, informatics and culture are aligned for continuous improvement and innovation.

This vision and its potential is central to the discussions here today.

To help marshal field leadership on the various dimensions important to progress, we formed several innovation collaboratives including one from which you'll hear in a few minutes, the Clinical Effectiveness Research Innovation Collaborative devoted to accelerating continuous learning from routine care delivery.

Several participants in that collaborative, including some here today, put together a statement to be introduced by the collaborative co-chair Dr. Richard Platt which, although not an endorsed position of the IOM, has grown out of collaborative discussions.

My second point to underscore is the centrality of information from standard of care interventions to the vision of continuously learning health care system in which every health care interaction is also an opportunity for learning and improvement.

The notion of continuous evaluation and improvement is not novel.

It's standard practice in successful businesses as illustrated by systems such as Six Sigma, and lean processing. In health care with many variables in play and much variation in individual responses, improvement requires continuous monitoring and assessment of both the content of care, delivered and the processes by which it is delivered.

This is the essence of continuous learning and even in this early stages, the potential has already been demonstrated.

Examples have been referenced throughout the course of the day's discussions.

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Throughout these examples, data that are accessible and reliable represent the currency of continuous learning.

Timely use of this data for learning faces serious regulatory, technologic and cultural challenges.

As the participants from CERIC discussed in greater detail, a regulatory philosophy that effectively penalizes the gleaning of generalizability knowledge from routine care can distort the opportunity for broader learning.

This brings me to the third point.

Implicit in the vision of continuous learning health care is the acknowledgment that research and practice can no longer be viewed as sharply discrete realms but rather should be viewed as interrelated elements in a continuous cycle of knowledge generation, application, and positive change.

That is why this moment, this conversation about standard of care research and associated policies and practices, is so central to the cadence of health care improvement.

Progress in health care as with progress in any field, requires the acknowledgment that current practice isn't perfect.

That health care systems growing capacity for continuous learning and evaluation will inevitably expose uncomfortable truths about the risks associated with routine accepted medical practice.

But the risk of ignorance of practices perpetuated without reliable evidence, cannot be ignored.

The IOM pointed out over a dozen years ago to err is -- to err is human but errors can be prevented.

As our responsibility to apply the capacity to improve the practice of medicine and health of patients everywhere.

As a nation, we have a hand the tools to stem the flow of missed opportunities for care improvement.

MODERATOR:

Your seven minutes are up.

MICHAEL MCGINNIS:

Thank you.

MODERATOR:

We start with FDA.

ROBERT TEMPLE:

Thanks.

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No questions.

MODERATOR:

NIH.

KATHY HUDSON:

Thank you.

I appreciated your comments.

I don't have any comments.

MODERATOR:

OHRP.

JERRY MENIKOFF:

Thank you Dr. McGinnis.

One question, so when you were talking about the collaborative and quoting in the comparative effectiveness studies, such as those comparing routine interventions within the general standard of care would not trigger IRB approval requirements.

I wonder if you could elaborate in terms of, and if it's not your view, that's fine, what exactly is that getting at?

If for example that would cover studies such as SUPPPORT?

Is the point of that, because you don't need IRB approval, we are going to change the consent process? So if you could explain more what you're actually proposing.

MICHAEL MCGINNIS:

The general assumption behind that particular statement is that the regulatory process would be focused on the issue of the level of risk involved as opposed to the nature of the study.

JERRY MENIKOFF:

So would you need consent?

MICHAEL MCGINNIS:

In this particular study?

JERRY MENIKOFF:

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Or so you're saying that other process would be what would be -- to determine what type of consent you need and if you needed it at all?

MICHAEL MCGINNIS:

Yes.

JERRY MENIKOFF:

Some alternative process to the IRB process?

MICHAEL MCGINNIS:

The.-.First I should emphasize that I don't want to get into --

[Multiple Speakers]

The assumption is that if the risk involved does not pass a certain threshold, there would be an alternative approach to addressing the conduct of the work.

JERRY MENIKOFF:

O.K. Thank you.

MODERATOR:

FDA?

ROBERT TEMPLE:

Even in a trial that randomized individuals, if they were -- if both interventions were similar, and relatively low risk, you can contemplate such a trial would be randomized without getting consent?

MICHAEL MCGINNIS:

Again, I want to emphasize this is a personal statement but I can certainly see, personally, that in a situation in which the anticipated risks are various interventions under study, had essentially no distinctions, that were anticipated, then yes, randomization as a personal opinion, could be a normal course of the delivery process.

MODERATOR:

Thank you.

PRESENTER: RICHARD PLATT

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RICHARD PLATT:

Thank you. I'm here on behalf of 47 of my colleagues from 33 institutions who are participants in the CER innovation collaborative of the IOM that Michael McGinnis just described.

These opinions are our personal opinions, however, not the Institute of Medicine's.

Let me start by summarizing our headline thoughts.

The first is that learning what works to achieve better health outcomes must be central to the mission of every health care organization. And that there must be full transparency for the public and for patients about those learning activities.

And the second is that regulations and incentives must support rather than inhibit such learning activities.

Let me use --and I'll also say that as the 25th speaker of the days events, that virtually all of my colleagues points have been touched on today. So, I'll use this opportunity to underscore the ones that we agree with.

Let me set this up with a hypothetical case which is based on our real life experiences in the last two or three years. So imagine a hypothetical hand hygiene product called Soft Clean, that is intended to replace soap and water for hand washing in hospitals by health care personnel and by visitors to the hospital. The active ingredient is marketed without prescription but Soft Clean itself is FDA approved for use on surgical services. It is advertised to be easy on the skin of the people who use it and to have excellent antimicrobial properties.

Hospital A adopts it throughout the hospital and hospital B is undecided about whether to use it. After using it for sometime, hospital A wants to gain some sense of whether this is beneficial product. It realizes that it is not large enough on its own to make that assessment and so it polls hospitals across the country and it find 50 that have adopted it and 50 that haven't adopted it. And these 100 hospitals pool their experience with the intent of learning how well it works and they are disappointed to find that it is really impossible for them to learn anything useful.

That is partly because they didn't have a standardized way of collecting their data. But it is also because on the reflection, the 50 hospitals that adopted it are systematically different from the 50 hospitals that didn't. So there is no good way to compare their experience.

Hospital B, on the other hand is interested in making a decision about whether to adopt it and it finds 100 hospitals that are also thinking about whether they should adopt this product. They agree that 50 will adopt it immediately and the other 50 will wait and all 100 of them use the same methods to collect and categorize their experience. The results are that they find that people who use the product to clean their hands, in fact, experience substantially fewer problems, skin problems, with frequent hand washing, and more importantly, the patients in the hospitals that adopted this product experience substantially fewer infections.

The conclusion is very useful to these 100 hospitals but it is also useful to everyone else. So it's a simple example. It raises a number of issues that are problems with the current regulatory framework. I'll mention three of them.

The first is the great difficulty in distinguishing between high-quality, quality improvement activity and research activities. I think many of us are recognizing the tension between good quality, between doing good quality quality improvement and doing research. It is unclear for instance whether unaffiliated hospitals can participate in joint quality improvement initiatives. It may be clear in the regulations but it's not clear to many institutional review boards.

Randomization is clearly the best way to enter this question and that is typically a criterion of research. Randomization at the level of hospitals as in this case or in other units of care can only really be effectively performed with waiver of informed consent.

Now some assert that randomization itself precludes waiver of consent. Others would say waiver consent could be waived with a minimal -- if the study confers minimal risk and we've already talked today about the fact that -- under some interpretations it is impossible to conduct studies of critically ill patients such as those in intensive care units, under the minimal risk provision.

And finally, as Dr. Temple has pointed out, the FDA has no provision for waiving consent and you should say why should the FDA be involved in this particular example I gave? The product happens to be approved for use in surgical services but not in general hospital services so the fact that it is used hospital wide is not in strict accordance with the FDA approval.

Finally, the fact that the regulations that are appropriately designed to protect vulnerable populations like prisoners, can be a substantial barrier to doing studies in hospital populations where these vulnerable populations may be incidental, minor participants in this study population.

From these and other kinds of experiences, the collaborative's members have drawn seven kinds of lessons and I'll share them with you.

The first is the one I have already mentioned that learning should be woven into routine care under conditions of full transparency.

The second is that both over regulation and under regulation of learning activities can increase risk for patients.

Third is that oversight should be calibrated to incremental risk compared to care that would otherwise be delivered.

Fourth, privacy protections should be calibrated to patients' expectations and to incremental risks.

The fifth is that assuming there is appropriate protection of privacy and confidentiality, oversight should not impede coordination between otherwise unaffiliated organizations.

Six, widespread dissemination of lessons from these kinds of activities should be encouraged. OHRP staff created this transcript from the video captions by correcting transcription errors and identifying the speakers.

And finally, we need to better understand patients and the public's expectations about learning activities as part of the routine delivery of care.

We have three recommendations that we believe to be implemented under current regulatory framework.

The first is, we believe there will be great value in OHRP, Office of Civil Rights and the FDA providing much more complete and coordinated guidance about activities that are permitted under existing regulations.

MODERATOR:

Your seven minutes are up.

RICHARD PLATT:

Thank you. The second is that we should broaden the definition of health care operations as used in the context of HIPAA regulations and it will be worthwhile to assess patients and the public's expectations about learning activities.

We also believe that new regulations should build on an ethical framework that includes responsibility of health care providers and systems to learn and to improve care.

Thank you.

MODERATOR:

Thank you. I'll start with FDA.

ROBERT TEMPLE:

Probably no real questions. I assume that many of these interventions would be so called cluster randomized interventions?

RICHARD PLATT:

There are lots of reasons that that is the preferred way to do this.

ROBERT TEMPLE

As your example was.

RICHARD PLATT:

Right.

ROBERT TEMPLE:

And certainly in those cases, we all recognize that we are thinking about it. Individual consent becomes unrealistic.

Maybe something posted on the door, but other than that...

So I think that -- What other impediments -- so that's one --

RICHARD PLATT:

We might all recognize it but it is a substantial barrier to doing a large number of highly relevant studies that would improve outcomes.

ROBERT TEMPLE:

Because for our drugs, anyway, there is no way to waive consent now. Even for us.

RICHARD PLATT:

But beyond that, I think that many institutional review boards do not see a clear path to waiving consent because of issues around minimal risk or just uncertainty about whether they will be second-guessed. That's the reason we think there can be great value in essentially creating a body of case law that can serve as precedent for IRBs so they can understand what is acceptable and what isn't.

Otherwise they, for understandable reasons, tend to be very conservative in what they'll approve.

ROBERT TEMPLE

But again, you're mostly thinking about cluster randomization --

RICHARD PLATT:

I think that is a very common situation in which we could make progress quickly.

MODERATOR:

OHRP?

JERRY MENIKOFF:

Thank you Dr. Platt. This is very helpful.

I too, this is more of a comment but we appreciate being able to work with you and your colleagues on all of these issues. As you know, we are continuing to do that with FDA, with NIH. We recognize that the system should be flexible and there are important types of studies that can be done in the future and some of them can involve waiver of informed consent and we look forward in particular to drawing the collect lines, that there are some studies where we still do need informed consent as issues raised regarding SUPPORT have noted. On the other hand there are other studies that can be done without informed consent and it's a question of drawing the right lines.

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But we recognize the importance of doing that and look forward to moving forward with clear guidance and other appropriate changes as others know we do have our advanced notice of proposed rulemaking, which is moving forward.

MODERATOR:

NIH?

KATHY HUDSON

So I want to make sure I understand. So for cluster randomization, you're suggesting that some institutions and IRBs at those institutions are hesitant to adopt an approach that would waive consent because of an absence of clear guidance or the concern about being second-guessed, I think was the word that you used?

So with that, would that be alleviated by some utterances by OHRP about the conditions under which a waiver of consent would be acceptable and then secondarily, Bob talked about posting something on the door.

I was wondering if your collaborative addressed the virtues of posting something on the on the door to let patients know –

RICHARD PLATT:

So we think a variety of kinds of mechanisms for informing study participants makes sense. That includes putting notices in patients' rooms. But more than that, we believe that it would be appropriate for organizations to have a publicly accessible roster of the learning activities they are involved in so that -- by analogy, many organizations tell their patients in advance, we are a teaching organization, and as you're receiving care, some trainees will be involved in your care. We'll always tell you who they are.

We think that kind of model may be an appropriate one saying, as a general proposition, we engage in learning activities. Here are the learning activities we are involved in.

KATHY HUDSON:

One last question. You talked about the regulations, protection of prisoners and other vulnerable populations potentially standing in the way of important research involving those populations, especially when they are in the hospital setting. But you don't -- I didn't see sort of a recommendation for how to, or what your recommendation is --

RICHARD PLATT:

I think the recommendation would be if vulnerable populations are only incidental members of a study population, then the regulations that govern the general population should apply, not the ones that apply to the special populations.

KATHY HUDSON

Thank you.

MODERATOR:

Thank you.

PRESENTER: ANN BONHAM

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ANN BONHAM:

On behalf of the AAMC, I thank you for the consideration of this issue.

In the context of what AAMC believes and is committed to patient-centered and evidence-based care, as a general principle, an IRB should be provided with and consider the currently available evidence for assessing the risk of research and for ensuring the understanding and the protection and privacy of human research subjects.

In that general context, I'll make five points we would like for the Department – points that we would like the Department to consider.

The first point is that both the IRB and the potential research subjects should have a clear understanding of the likely outcomes that are inherent to the condition -- inherent to the condition or disease progression and associated with the known standard of care intervention, and those outcomes should not be necessarily attributed to being part of a research protocol.

The second point. In considering the disclosure of reasonably foreseeable risks, the IRB should have clear guidance to help them determine whether an intervention involves treatments in common practice, and whether the choice of intervention is one that is typically discussed with patients rather than depending on whether or not the patients are part of the research protocol.

The third point is that uncertainty about the risk of various standards of care intervention is often the driving force behind conducting the study and does necessitate the research.

Where there is no consensus in the field that one intervention is preferable over another like in the SUPPORT study, the likely variation in outcomes is the fundamental purpose of the research.

Not a risk of participating in the research.

And in fact, the undiscussed risk of standard of care treatment for a patient is when a physician has no decisive evidence on which to base the recommendation of one intervention over another.

Randomization shouldn't be considered a risk in those case where is providers do not have sufficient knowledge and this point has been made by others, about the differences in the risk or effectiveness of the interventions.

Physicians routinely choose one or the other treatments based on training, clinical judgment, and local norms.

And essentially this is an organic randomization.

When decisions are routinely made no different to interventions, research that incorporates randomization may not pose any additional risks.

And finally, without essential comparative effectiveness research like that represented bite support study -- by the support study, physicians are forced to use anecdotal information or rely on the customs they used as trainees to make clinical decisions.

It's our job as a community to work together to ensure that we are creating an environment that encourages the learning and knowledge in such research.

At the same time, empowering patients to participate in this process and encouraging their protection. Coming together, we are leaving physicians in this unattainable position of taking a reasonable guess instead of ensuring that all patients receive treatment based on the best possible evidence.

So, in our thinking about this, let's not push patients away from research to greater risk treatments for which there is little or no evidence.

Again, thank you to the Department for the consideration of this serious issue.

MODERATOR:

Thank you. OHRP?

JERRY MENIKOFF:

Thank you very much. So just to clarify my understanding of what you think an appropriate consent form in terms of these two elements of standard of care should say.

Assuming one of the things somebody might be reassigned to per randomization is different than they would have otherwise gotten, should they be told about how the risks of that treatment differ from what they might otherwise have gotten?

ANN BONHAM:

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So, we think that the standard should be that the patient or the research subject, should be informed of the standard of care, the risk and benefits of the standard of care treatment and that should be the guiding principle, not the fact that they are being part in the research protocol.

JERRY MENIKOFF:

So the consent form, in other words, doesn't have the information?

ANN BONHAM:

I think it should be that the consent should be the same as considering what you're sharing with the patient in the standard of care issues because in the standard of care, you may be choosing like a SUPPORT trial, one range or the other and that should be made very clear.

So there shouldn't be a different standard because you're attaching a research protocol to it.

The premise should be that all -- it should be transparent so patients clearly understand the risk and benefit of the standard of care they are receiving.

JERRY MENIKOFF:

Okay.

Maybe I'm just not understanding this.

The premise is then you are changing what portion of this standard of care or which element of standard of care a person is getting and so a lot of people, I think, if they were asked to be in these trials want to know the differences between those particular items.

I'm not sure how it makes sense to say this.

ANN BONHAM:

While I don't disagree, I think the same premise should be applied when choices are being made without the research protocol that intervention, differences should be made clear in that case also.

JERRY MENIKOFF:

Okay.

I understand that part.

Thank you.

MODERATOR:

FDA?

ROBERT TEMPLE:

The AAMC sounds committed to making sure that they understand the treatments. That sounds fine.

What about the aspect of it that is the reason you're doing this in the first place?

You're trying to find out whether one of them is better than the other.

And let's say it's a bad disease.

So it matters whether one is better than the other.

And you're also -- and they value side effects of various degrees but you never had a good comparison so you don't know.

Isn't telling someone that one of them might turn out to be better than the bad disease or worse, of course, and might have more of some unpleasant side effect, part of what you're telling them?

You're not telling them you know it, but it's one of the possible outcomes?

ANN BONHAM:

I think that is correct and this also should be the case when you're providing a treatment or suggest the treatment in the absence of being a part of a research protocol, you should also have those same kinds of conversations.

And that should be the driving principle.

ROBERT TEMPLE:

Don't disagree, but nobody regulates that.

MODERATOR:

Thank you.

KATHY HUDSON:

So I have a question about your first point in terms that the IRB should have clear guidance to help determine reasonably foreseeable risk.

And I think that this has been sort of come up recurrently over the course of the day.

I think that the SUPPORT investigators have made the point that the evidence at the time that the SUPPORT trial was undertaken suggested that there was no difference in mortality at the lower and higher oxygen range.

That was the understanding of the NIH as well.

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And that was a standard of what is reasonable, foreseeable risk in terms of evidence.

We talked about there being a debate out there, that there was worry.

Bob talked about the possible outcomes and so I'm interested in sort of AAMC's view or your personal view about, do you need published studies?

Or meta-analysis?

Or is it a general consensus view that is sufficient to trigger what is a reasonably foreseeable risk?

Or should be a reasonably foreseeable risk that should be disclosed?

ANN BONHAM:

So no question that the definition of reasonably foreseeable risk has been under considerable debate.

And I think when we talk about the best possible evidence, sometimes that is empirical evidence.

Sometimes it's clinical guidelines.

Sometimes it's expert opinion.

So I think as long as there is some consistency and clarity across the agencies to the clinicians and the scientists, that would be very helpful.

We may not all agree on the bright line but as long as we are having some consistency in defining that white line, it will be much clearer and put us in a better position than it is now where retrospectively, we are looking back over our shoulder and saying, well, was that or was that not minimal foreseeable risk?

Rather than coming to some kind of agreement prospectively.

KATHY HUDSON:

Can I ask a question about that retrospective point?

So your third point is we not look back.

I'm wondering, are you thinking there should be a statute of limitations on second-guessing a study, the SUPPORT study was concluded and published and well over by the time that the investigation was undertaken?

Or are you suggesting we really needed to ask these questions in 2002?

ANN BONHAM:

I think that both are correct.

Any time one is looking back and making a judgment, that say different consideration than making a judgment prospectively.

Learning that we have from this is getting clarity of guidance from the agencies about what should be happening prospectively.

And I think always looking back, it's a different view.

Looking in the rear view mirror is a different view than looking forward.

So while we learn from it, I don't think we make our judgment based on looking back.

MODERATOR:

Thank you.

ROBERT TEMPLE:

We also would like a statute of limitations on second-guessing our approvals.

[Laughs]

PRESENTER: ROBERT CALIFF

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MODERATOR:

Robert Califf.

ROBERT CALIFF:

Appreciate the opportunity to be here. It's tough being the last speaker and going up against the President, I guess. I'll do my best. And I think everything that I was going to say has already been said.

I do have written comments. They do represent my opinion, not the opinions of organizations that I'm funded by, or associated with. So what I'll do, I'll take the liberty in my seven minutes to give a few opinions about what has been said and maybe emphasize certain points.

Now, I'm going to divide these into things that probably almost everyone agrees with some things that maybe most people agree with and some things which are very controversial.

I bet most people here would agree that most Americans think they should be told when they are in a study. And I think that's a fundamental issue, and whether that is considered consent or notification and how it's done is a matter that I hope you all will work on over the next few months.

Second, SUPPORT probably would have been better off, better served if it had use in the New Zealand consent. Whether you call it a primary aim of the study or a risk of the study is arguable. But the fact that mortality was being looked at, I think for most of us, it is something that we would have liked to have known.

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Thirdly, most of us would prefer to have a doctor than nothing at all. But I would also argue that most of us would like to have a doctor well informed with evidence and a doctor who's making the best guess based on what he or she learned in residency.

Now a little less likely and maybe a little controversial, every clinical trial is a compromise. I have been probably designed and been involved in as many clinical trials as anybody at this point. But if you show me a great clinical trial I'll show you 100% of investigators and leaders who thought it could have been done better looking back. Because we have to get literally dozens to hundreds to maybe even thousands of people to make compromises to agree on a single protocol so we can answer a question.

I have also noticed that the Monday morning quarterbacks that you just discussed tend to be most vociferous if they are not the people who are actually designing the trials and having to put their money down on what they believe before the study starts as opposed to looking backwards through the rear view mirror, as you put it.

I doubt that many people believe that the SUPPORT investigators of the SUPPORT study was unethical. But I say this also in the context of my previous point that almost 100% of the people probably could see a way the SUPPORT study could have been done better or the consent form could have been better but that is also true as I say of every clinical trial that I have ever been involved in.

And sensational claims of calling people unethical I think really detract from the serious discussion that needs to occur.

Now to the hard stuff.

First of all, I want to take exception to what Dr. Annas said to start with. I think the healthiest outcome of this meeting could be a healthy skepticism about how much doctors actually know when they are making the choices over treatments when there is no firm evidence.

I don't say that in any way as someone who ran an intensive care unit for 20 years to paralyze doctors and cause them not to make decisions or for patients not to have confidence. But somehow in this national discussion, we have got to help the public, individual patients, and doctors and hospitals come to grips about the with the fact that we often do have uncertainty. We are not sure what to do. We are making a guess, and I think we would be better off if we all recognize the uncertainty and try to quench the uncertainty and stop the uncertainty as much as we could so we make good decisions behalf of our patients.

Secondly, I really love the transactional risk presentation. I spent a good part of my career studying the effects of chaos and decision-making. It is inappropriate to call it random. It's not random decision making that goes on.

Decision-making happens for a lot of reasons. Sometimes actually because of the characteristics of the patients but often for many other reasons and I think we are very well laid out in the that presentation.

But there is another type of experimentation that goes on every day in this country that is called quality improvement and Dr. Platt and I have many healthy arguments about how we should view that. But almost every health system in the United States is systematically varying patterns of care and measuring very carefully not necessarily with clinical outcomes as a primary end point, often with finances as a primary outcome. Without consent and without notification of what is being altered and what is being withheld from the options that patients have.

And the idealistic view of fiduciary responsibility of physicians, I think now really needs to be called into question more and more as the majority of American physicians are employees of corporations, either hospital corporations or health systems or large practices that restrict and dictate what options made available to patients.

And it's in that context that I agree with Dr. Bonham that when we are talking about risk, I really believe it is important that we inform the public and people thinking about clinical trials, that there are significant risks in being exposed to standard practice relative to protocols.

The best evidence on this as shaky as it is from a Cochran collaboration study, the highest form of evidence we have, it is not definitive but all the trends are in favor of better outcomes of people that participate in clinical trials as compared with people with usual care.

We should also acknowledge that when we call special attention to research in ways that are very expensive, cost should not be the primary driving factor but we are pushing many investigations into a subterranean arena that is called quality improvement and I wish Dr. Kass had more time because she could have told you about the qualitative research where many people embedded in health systems said we are doing research but we call it quality improvement because we don't want to be exposed to the mandatory 19-page consent form.

So the last two things I want to emphasize here, I wish we had more discussion about modified consent. One of the issues about minimal risk is that it not only allows you to waive consent which I think shouldn't be done all that often, actually. But it allows you to modify consent to make it reasonable.

Time after time in empirical research when patients have been asked, they said, please don't give me the 19-page form. Give me a single page and then give me a way to find out about additional things if I possibly can.

And then finally, randomization itself needs to be a focus of intense energy in terms of education. Providers have as much difficulty understanding randomization as patients in my experience.

MODERATOR:

You're seven minutes are up.

ROBERT CALIFF:

Thank you so much.

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My final two points involve patients and their families as much as we possibly can in research. We heard it in the New Zealand study. It is critical and lastly, empirical research I think can resolve a lot of these issues. We will find the American public is a lot smarter than we give them credit for if we involve them and find out what they want and then give it to them.

Thank you.

MODERATOR:

NIH?

KATHY HUDSON:

No questions. Thank you very much.

MODERATOR:

FDA?

ROBERT TEMPLE:

That was a great summary.

MODERATOR:

OHRP?

JERRY MENIKOFF:

It was a great summary and we look forward to working with you and your colleagues as we move forward.

ROBERT CALIFF:

Thank you.

MODERATOR:

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There was a scheduled wrap-up and I think Robert Califf took care of that very nicely.

It has been a very long day. And once again, we are grateful to the presenters for being very thoughtful.

Many submitted highly detailed, written comments for the record. Those are available and you really stuck to your time. So thank you. You made this a very, very productive day for us.

I'm going to take about 15 minutes to run through, we had several comments submitted

before the deadline and we had indicated we would summarize those comments.

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They also are available online.

But several folks worked through and tried to pick three to five high points of each of those comments just in respect to people who got submissions before the deadline.

We're not -- and they were not able to be here today.

So Gerald Schatz reminds us as an ethical matter, it's well to remember that clinical equipoise is very difficult to demonstrate and does not in itself justify either research or shortcutting of human subject protections.

And two, perinatal research almost always involves clinically fragile subjects, emotionally fragile parents or surrogates and circumstances not conducive to understanding or to voluntariness.

As a procedural matter, remember that data and safety monitoring entities have a duty of safety and data analysis and that research be reviewed for safety problems as frequently as is appropriate.

As a legal matter, it is well to remember the statutory intent of human subjects protection regulation, quote, "to protect human subjects of research at 42USC-section 29A."

Mark Hochhauser submitted two sets of comments.

One set focused on readability and comprehension and the other on costs.

And these, again all of these comments, full comments are in the record.

On readability and comprehension, all of the IRBs recommended that consent forms be written at a six to eighth grade reading level.

However, none of the SUPPORT forms met those recommendations.

Inadequate disclosure of study risks is certainly a significant concern but so are risks that are disclosed but not comprehended.

None of the eight SUPPORT consent forms, all drafted by significant research institutions and reviewed by IRBs, demonstrate significant concern for readability or comprehension.

The OHRP and Public Citizen criticisms of the consent forms say nothing about the issue either.

So we have a clear demonstration that understandable consent forms are not a priority for the clinical research enterprise.

And then focus on costs.

Three key points.

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Almost all of the consent forms stated no additional costs for participating in the study, but the subsequent research-related injury cost statement shortly after that statement contradicts the sentence by stating how research-related injury treatment costs would be billed to the mother's insurance company or to the mother directly.

His comments in italics highlight relevant language that is contradictory, that is hard to understand and inconsistent with FDA guidance and we would just point you to his submission, because it is far too detailed to go into here.

Evelyne Schuster, again, three key points or two key points and recommendations.

The multiple informed consent documents and multiple revisions from the 22 institutions involved in the study make no mention of death and do not even suggest that death, with ROP or without ROP, is a key endpoint of the study.

But research is not treatment.

Emphasizing their similarities is misleading.

Her recommendations: in research as in treatment, all reasonably foreseeable risks to persons, including especially any risk of death, should be disclosed and explained to ensure the quality of the informed consent.

Two, in assessing the risk-benefit ratio of a research project, IRB members should be reminded that the rights and welfare of subjects are not negotiable.

IRB chairs should appoint a member to focus exclusively on the risk benefit ratio of a research project with special attention to those who pose any risk of death or permanent disability.

And three, the role of the appointed IRB member will be to establish how the risk benefit ratio of the research project is favorable based on high quality, competent and reliable scientific evidence, review of the scientific literature, and the protocol itself.

Peter Aleff submitted several forms of commentary, each one an update of the other but five key points: Keep medical researchers from using your children as disposable guinea pigs as they did in recent preemie suffocation experiments.

The designation standard of care intervention is a red herring because each intervention to be tested differs by definition from the prevailing standard of care and carries different risks.

The idea that physicians are allowed to lie for a greater good invites the hubris that justifies deception for the purposes which only the medical uberman can judge.

Although the SUPPORT researchers had clearly violated all relevant U.S. regulations and international codes of medical ethics, the OHRP backed off from even the mild slap on the wrist it issued to the knowingly preemie suffocating experimenters.

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Presenting such questions as new, and still needing answers, looks merely like an attempt to obfuscate the breaches and imply a lack of clarity where the answers are already well defined.

Ross McKinney, four key points.

The risks associated with uncertainty in routine clinical practice have been underappreciated, the risks associated with standard of care research overstated.

Clinical care in the context of research is often less risky than arbitrary decisions made by individual clinicians.

No patient should be enrolled in standard of care clinical research without agreeing to participate in the research with a thorough understanding of the specific inconveniences and loss of flexibility that come with the research protocol.

This agreement need not require a lengthy consent document and at times might be oral, which in and of itself is one degree more restrictive than the routine in clinical care.

If the -- Number three, if the research comparisons are within standard of care, using currently approved therapies within their approved indications, and are judged by an IRB to be in equipoise, there is no need for discussion of research-related medical risks in a consent document.

Number four, the standard for no more than minimal risk interventional research should be comparison with individuals with the similar state of disease or health and prognosis rather than healthy individuals.

Raymond Hutchinson proposed several points for consideration as well.

In the risk section of the research informed consent document, the risks which are uniquely different between the standard of care interventions either in occurrence or severity, should be the primary focus.

Reasonably foreseeable risks include those reported in multiple publications in the medical literature in association with the specific standard of care intervention.

The level of medical certainty for evidence-based risks should be evaluated, assigning more credibility to risks associated with published, randomized, control trials, than in the order of decreasing credibility with large retrospective series, case reports or physician impressions.

Third point, the risk of death, if present, should always be listed in the informed concept document.

Other risks occurring in five percent or more of patients are reasonably foreseeable and should be listed.

Fourth point, equipoise for the standard treatments being compared must exist when simultaneously weighing risks and benefits for each standard arm.

And five, suggest waiver of informed consent not be an option for standard of care interventions even when the differential risks between or among them is minimal, if the risk of the interventions themselves is high.

For example, when comparing two evenly-balanced risky chemotherapy arms in cancer treatment.

And finally, Nancy King has submitted several key points as well.

Randomization poses a risk that should be considered and disclosed.

The way in which a research subject is chosen to receive an intervention is clearly distinguishable from the way a patient's treatment is determined.

Randomization alters the risk of harm to which the patient subject is exposed in comparison to standard of care treatment.

Assignment to an intervention arm often dictates less flexibility in response to empirical evidence than is often available and what is practiced when a patient receives standard treatment.

The uncertainties associated with standard treatment, the very reasons comparative effectiveness research and other research involving standard of care interventions are being done should not be permitted to mask full consideration and disclosure of the foreseeable risks in the range of risks that may be at issue in such research.

Some investigators complain they are required to tell subjects more when they are doing research than they tell patients when they are treating them.

The right answer is not to lower the bar for disclosure in research.

The right answer is to raise the bar for disclosure in treatment.

So that summarizes the comments that were received and we had indicated we would summarize in today's meeting.

We have received comments from about 40 individuals.

The comments docket remains open and we encourage you, those of you here today, those of you viewing, and all of our wider circle who might have an interest to comment up through the closure of the comment period.

That comment period closes September 9.

So people who couldn't attend or want to send additional comments, OHRP's website is the handy place to go but you can also go to [regulations.gov](https://www.regulations.gov) and insert the docket number.

And I can read that to you if you want it but it's late in the day, it's there.

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We'll provide that if you need it.

It will be on the webcast so folks can access that as well.

So we heard from a lot of different people today with very different views on a critically important issue.

And their next step will be to review everything that we heard today.

And the comments yet to come, those that come in by the deadline.

It truly is an important issue.

We knew that.

We heard that clearly today.

It has never been a question of how important this is and how thoughtfully we need to consider the time you took, the comments you made today to help us sort through key and critical issues that we can address with future guidance.

So it will take time.

It is not going to happen overnight.

All the presentations and comments will be on OHRP's website and the transcript as I mentioned earlier, will be available by close of business tomorrow.

And the archived version of this webcast will be posted and will be available probably within about a week.

So, lots of people to thank.

First and foremost, you.

Whether you presented or whether you didn't, whether you were viewing the entire day via webcast or tuned in and out as your schedule permitted, your interest and your thoughtful comments and, I know the lively discussions that were happening, are really, really helpful to all of us.

So thank you.

Presenters particularly, because it took an extra measure to take things that you care very passionately about and condense that into seven minutes.

And then be in almost a murder board experience here with the panel.

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But it went well.

We got some excellent, excellent points, I think, clarified that will help us in our discussion.

Others to thank.

First of all, the HHS video production team and the web team and communications team who made so much of this possible.

And they are often invisible.

Their job is to be invisible and they are not thanked because they are so invisible but I believe in thanking them.

So we are really grateful for their assistance.

The logistical support staff, the contractors who kept things moving well, and handled so much of how this meeting was organized.

The panelists.

We have had very little time together as a panel team, and it was just amazing to me to see the way you complimented each other and everyone had read everything, we made sure they had all the documents, the presentations, the comments.

They spent all their free time in the last four-five days camped out with the information reading it.

And it really showed.

They were well prepared with questions and again, I think that it really is going to help us all moving forward.

And last but not least, Irene Stith-Coleman who sat over here running the timer.

She really was the wheels behind so much of this from the generation of the public notice with the assistance of General Counsel and General Counsel is my best friend these days.

But Irene really just kept the grinding processing going and did them well, really, really without Irene I'm not sure we would have such a successful meeting.

So thank you, Irene for all you did and then for sitting here mindlessly pushing that button today, because that really required a lot of concentration.

Thank you.

So again, to all of you here, thank you, thank you for joining us online out there in web land.

Those of you watching this in the future, we hope you'll have a wonderful evening.

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Thank you again for your commitment, your passion and we are going to be moving forward.

Thank you.

[Applause]

[\(Return to Agenda\)](#)