

From: Carr, Sarah (NIH/OD) [E]
To: Patterson, Amy (NIH/OD) [E]
Subject: FW: Houston....we have a problem
Date: Thursday, April 24, 2014 8:59:04 PM
Attachments: Draft Talking Points for NIH Director 4-24-2014fd.docx

---

Is the revised last bullet better? I'll come in.

Kathy,

Here are draft TPs for FC's call with Corr. They recap the April 16th email and incorporate your points below a(b)(5)

Amy
-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 23, 2014 11:08 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Tabak, Lawrence (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: Houston....we have a problem

FC,

Standard of care (soc) is on your corr list for this week. (b)(5) (b)(5) I was nearly ready to propose to you that if we continue to get no response from ohrp, that we should just tell hhs that we will be proceeding with our workshop (that osp had originally planned to coincide with the public comment period for the draft guidance.) Then, I get the email (immediately below) from OHRP. Ivor, who has been acting while jerry was out, is unaware of any concerns you raised with bill about standard of care guidance!!! Repeat - (b)(5) (b)(5) (b)(5) I am very disappointed and sad. (b)(5) (b)(5)

(b)(5)

Common rule is also on your list (b)(5) so I would suggest you

not address that directly in this week's corr call.

Kathy

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 23, 2014 10:14 PM
To: Pritchard, Ivor A (HHS/OASH)
Subject: Re: Guidance following the SUPPORT Trial

Wow! This (that ohrp is unaware that fc has raised major concerns with Corr) is surprising and concerning. Something seems off kilter in communications channels.

While this works itself out, I appreciate very much our candid open channel of communication.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

> On Apr 23, 2014, at 9:43 PM, "Pritchard, Ivor A (HHS/OASH)" <Ivor.Pritchard@hhs.gov> wrote:
>
> Kathy:
>
> I was unaware of Dr. Collins' raising the issue with Bill Corr. I do remember your earlier proposal. (b)(5)
(b)(5) We are meeting to discuss a draft guidance document on Monday, and hope to send it out soon after that.
>
> Hope this is helpful.
>
> Ivor
> _____
> From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
> Sent: Tuesday, April 22, 2014 3:38 PM
> To: Pritchard, Ivor A (HHS/OASH); Menikoff, Jerry (HHS/OASH)
> Cc: Koh, Howard (HHS/OASH); Devaney, Stephanie (NIH/OD) [E];
> Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
> Subject: RE: Guidance following the SUPPORT Trial
>
> Hi Ivor/Jerry,
>
> I am checking in on where things stand with the standard of care draft guidance. I imagine you know that (b)(5)
(b)(5)
>
> As a reminder, we sent in comments on the first SOC draft guidance on Feb 12. Since that time we have proposed that the leadership in the department join together to provide an outline of what the policy should look like so that OHRP would have a clear framework to guide your efforts. On

April 1 you declined and offered that a new draft would be forthcoming in "weeks."
>
> Francis has this topic on his agenda to raise - again - with Bill this week and I was hoping I might be able to provide a meaningful update for FC in advance of that meeting.
>
> Thanks,
> Kathy
>
> -----Original Message-----
> From: Pritchard, Ivor A (HHS/OASH)
> Sent: Tuesday, April 01, 2014 12:56 PM
> To: Hudson, Kathy (NIH/OD) [E]
> Subject: RE: Guidance following the SUPPORT Trial
>
> Kathy:
>
> (b)(5)
(b)(5)
>
> Let us know when you want to talk about the workshop.
>
> FYI, Jerry is back from leave.
>
> Ivor
>
> -----Original Message-----
> From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
> Sent: Sunday, March 30, 2014 10:53 AM
> To: Pritchard, Ivor A (HHS/OASH)
> Subject: RE: Guidance following the SUPPORT Trial
>
> Ivor,
>
> One more good faith effort is probably worthwhile. Do you have a sense of timing on when a next draft might be circulated to the agencies?
>
> As for the workshop, we will get back in touch with you on the specific role(s) for OHRP. We will certainly welcome input and participation from everyone in HHS but will reserve the primary organizing role.
>
> Kathy
> -----Original Message-----
> From: Pritchard, Ivor A (HHS/OASH)
> Sent: Friday, March 28, 2014 10:28 AM
> To: Hudson, Kathy (NIH/OD) [E]
> Cc: Koh, Howard (HHS/OASH)
> Subject: RE: Guidance following the SUPPORT Trial
>
> Kathy:
>
> (b)(5)
(b)(5)

>
> Regarding the workshop, we are aware that there is something in the works, but not really what. Do you have anything in mind for OHRP's role in planning the workshop, as well as participating in it? (b)(5)
(b)(5) Anyway, if and when we should be talking to anybody over there about the event, let us know.
>
> And thanks for the compliment about the OSTP meeting; I'll pass it along to Julie. This is going to be an adventure.
>
> Ivor
> -----Original Message-----
> From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
> Sent: Thursday, March 27, 2014 5:14 PM
> To: Pritchard, Ivor A (HHS/OASH)
> Cc: Koh, Howard (HHS/OASH)
> Subject: Re: Guidance following the SUPPORT Trial
>
> Thanks so much for the note Ivor. (b)(5)
(b)(5)
>
> What do you think about that idea?
>
> Also, as you know, nih will be hosting a workshop to talk about the issues in the guidance when it is out for comment. I hope you and your team will be able to participate - esp in the opening bits to lay out the draft.
>
> Finally, I thought you and Julie did a great job co-chairing and presenting at the OSTP meeting on the common rule! It could not have gone better.
>
> Kathy Hudson, Ph.D.
> Deputy Director for Science, Outreach, and Policy NIH
> 301 496 1455
> kathy.hudson@nih.gov<mailto:kathy.hudson@nih.gov>
>
> On Mar 27, 2014, at 4:51 PM, "Pritchard, Ivor A (HHS/OASH)"
<Ivor.Pritchard@hhs.gov<mailto:Ivor.Pritchard@hhs.gov>> wrote:
>
> Kathy,
>
> (b)(5)
(b)(5) We got Jerry's input on the last draft (b)(5) and we're working on revising it. We'll let you know when we're ready to share another draft.
>
> Cheers.
>
> Ivor Pritchard
>
>

Draft

Talking Points for NIH Director for Call with the Deputy Secretary

Friday, April 25, 2014

(b)(5)

Carr, Sarah (NIH/OD) [E]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Friday, March 28, 2014 12:23 PM
To: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: FW: Guidance following the SUPPORT Trial

Hi Amy and Sarah - Another OHRP Guidance FYI that Kathy Abel has passed on. Not for distribution, but wanted you both to see it.

-----Original Message-----
From: Abel, Kathy (NIH/OD) [E]
Sent: Friday, March 28, 2014 12:21 PM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Guidance following the SUPPORT Trial

-----Original Message-----
From: Pritchard, Ivor A (HHS/OASH)
Sent: Friday, March 28, 2014 10:28 AM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Koh, Howard (HHS/OASH)
Subject: RE: Guidance following the SUPPORT Trial

Kathy:

(b)(5)

Regarding the workshop, we are aware that there is something in the works, but not really what. Do you have anything in mind for OHRP's role in planning the workshop, as well as participating in it? (b)(5)
(b)(5) Anyway, if and when we should be talking to anybody over there about the event, let us know.

And thanks for the compliment about the OSTP meeting; I'll pass it along to Julie. This is going to be an adventure.

Ivor
-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, March 27, 2014 5:14 PM
To: Pritchard, Ivor A (HHS/OASH)
Cc: Koh, Howard (HHS/OASH)
Subject: Re: Guidance following the SUPPORT Trial

Thanks so much for the note Ivor. (b)(5)
(b)(5)

What do you think about that idea?

Also, as you know, nih will be hosting a workshop to talk about the issues in the guidance when it is out for comment. I hope you and your team will be able to participate - esp in the opening bits to lay out the draft.

Finally, I thought you and Julie did a great job co-chairing and presenting at the OSTP meeting on the common rule! It could not have gone better.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov<mailto:kathy.hudson@nih.gov>

On Mar 27, 2014, at 4:51 PM, "Pritchard, Ivor A (HHS/OASH)" <Ivor.Pritchard@hhs.gov<mailto:Ivor.Pritchard@hhs.gov>> wrote:

Kathy,

(b)(5)

(b)(5) We got Jerry's input on the last draft just before (b)(6) and we're working on revising it. We'll let you know when we're ready to share another draft.

Cheers.

Ivor Pritchard

From: Devaney, Stephanie (NIH/OD) [E]
To: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: FW: Guidance following the SUPPORT Trial
Date: Thursday, March 27, 2014 4:57:25 PM

FYI Amy and Sarah

From: Abel, Kathy (NIH/OD) [E]
Sent: Thursday, March 27, 2014 4:57 PM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Guidance following the SUPPORT Trial

fyi

From: Pritchard, Ivor A (HHS/OASH)
Sent: Thursday, March 27, 2014 4:51 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Koh, Howard (HHS/OASH)
Subject: Guidance following the SUPPORT Trial

Kathy,

(b)(5)

(b)(5) We got Jerry's input on the last draft (b)(6) and we're working on revising it. We'll let you know when we're ready to share another draft.

Cheers.

Ivor Pritchard

Butler, Brenda (NIH/OD) [E]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Thursday, February 20, 2014 3:46 PM
To: Lewis, Caya (HHS/IOS); Lee, Noelle C. (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: OHRP Guidance and NIH comments
Attachments: Confidential OHRP Draft Guidance_AcceptedTherapiesFAQs_Jan22.docx; NIH Comments on OHRP Accepted Therapies FAQs 2-12-2014.docx

Hi Caya and Noelle –

Attached are the OHRP Guidance (FAQs) and NIH's comments

Steph

Stephanie Devaney, Ph.D.
Science Policy Analyst
Special Assistant to the Deputy Director for Science, Outreach, and Policy
Office of the Director
National Institutes of Health
1 Center Drive, Building 1/103
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Phone: 301-402-1994
stephanie.devaney@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

NIH Comments on OHRP's Draft Accepted Therapies FAQs

(b)(5)

Carr, Sarah (NIH/OD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 24, 2013 8:57 AM
To: Hudson, Kathy (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Carr, Sarah (NIH/OD) [E]; Hardy, Ann (NIH/OD) [E]
Subject: FW: NICHD Neonatal Research Network study
Attachments: 12.23.2013 OHRP memo.pdf

FYI

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, December 24, 2013 8:56 AM
To: Borror, Kristina C (HHS/OASH)
Subject: NICHD Neonatal Research Network study

Hi Dr. Borror:
In May 2013, OHRP requested copies of protocols and sample consent documents for all the interventional clinical trials being carried out through the NICHD Neonatal Research Network (NRN). I am enclosing the attached confidential memorandum as the Optimizing Cooling Strategies at < 6 Hours of Age for Neonatal HIE study has been closed to enrollment. If you have any questions, feel free to contact me.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health
Eunice Kennedy Shriver National
Institute of Child Health and
Human Development
Bethesda, Maryland 20892

CONFIDENTIAL MEMORANDUM

December 23, 2013

To: Office for Human Research Protections (OHRP) HHS

From: Rosemary Higgins, MD
Program Scientist for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network

Re: Optimizing Cooling Strategies at <6 hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy Study from the Neonatal Research Network funded by the NICHD

In May 2013, OHRP requested copies of protocols and sample consent documents for all the interventional clinical trials being carried out through the NICHD Neonatal Research Network (NRN). The purpose of this memorandum is to inform OHRP that one of those studies, the *Optimizing Cooling Strategies at < 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy* trial, has been closed to enrollment (b)(5)

(b)(5)

If you have any questions or wish additional information, please let me know.

Attachment

cc: Kathy Hudson, Ph.D., Deputy Director for Science, Outreach, and Policy, NIH
Sally Rockey, Ph.D., Deputy Director for Extramural Research, NIH
NICHD NRN Coordinating Center (RTI)
NICHD NRN Site Principal Investigators

RTI INTERNATIONAL Memorandum

December 6, 2013

OC TECHNICAL MEMO #27

TO: Network Coordinators
Network PIs

FROM: The Data Coordinating Center

SUBJECT: (b)(5) Optimizing Cooling Trial)

The NICHD NRN Optimizing Cooling Trial *(Optimizing Cooling Strategies at < 6 Hours of Age for Neonatal Hypoxic-Ischemic Encephalopathy)* (b)(5)

Safety: the overall in-hospital mortality rate thus far is 13% (43/324). Safety outcomes by group are as follows. (These data are as received at RTI by Dec 2, 2013.)

(b)(5)

(b)(5)

Cc: Rosemary Higgins, MD

Bartok, Lauren (NIH/OD) [C]

From: Carr, Sarah (NIH/OD) [E]
Sent: Tuesday, December 17, 2013 7:58 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Further info on OHRP SoC guidance

I spoke to Julie Kaneshiro to get a bit more information about the status of the draft SoC guidance. (b)(5)

(b)(5)

Is a joint meeting a viable option?

From: Carr, Sarah (NIH/OD) [E]
Sent: Wednesday, December 11, 2013 10:20 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: RE: follow up on OHRP guidance

Here's the update from OHRP on where the SoC draft guidance stands – they "will be able to pick it back up" after they hand the NPRM package in to ES next week. This contrasts with what we were told before which was that the timeline would be pushed back by the length of the furlough.

I can understand that the NPRM may be all consuming for them, (b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, December 05, 2013 8:41 PM
To: Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: follow up on OHRP guidance

Nope. (b)(5)

Kathy Hudson, Ph.D.

Deputy Director for Science, Outreach, and Policy

NIH

301 496 1455

kathy.hudson@nih.gov

On Dec 5, 2013, at 8:09 PM, "Patterson, Amy (NIH/OD) [E]" <PattersA@OD.NIH.GOV> wrote:

Kathy,

(b)(5)

Amy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, November 25, 2013 11:51 AM
To: Lewis, Caya (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: follow up on OHRP guidance

Caya,

I wanted to touch base with you again (b)(5)

(b)(5)

We know the furlough delayed OHRP's progress by a couple of weeks, (b)(5)

(b)(5)

We look forward to moving the process forward expeditiously as uncertainty continues to plague our researchers. We will comment quickly

Thanks,

Kathy

From: Lewis, Caya (HHS/IOS)
Sent: Thursday, October 17, 2013 4:09 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: OHRP

Kathy,

It's good to be back.

(b)(5)

Talk to you soon,

Caya

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, October 17, 2013 3:56 PM
To: Lewis, Caya (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: OHRP

Hi Caya –

Was nice to hear your voice this morning at OS staff meeting.

As we get back to our usual work, I wanted to share with you a summary of our concerns about the OHRP proposal for development of new guidance for standard of care research. You will recall a round of emails about this before the shutdown. (b)(5)

(b)(5)

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, November 25, 2013 11:51 AM
To: Lewis, Caya (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Subject: follow up on OHRP guidance
Attachments: Proposal for Guidance on SOC 9-26-2013.docx

Caya,

I wanted to touch base with you again about our concerns (summed up below) (b)(5)
(b)(5)
document?

We know the furlough delayed OHRP's progress by a couple of weeks, (b)(5)
(b)(5)

We look forward to moving the process forward expeditiously (b)(5)
(b)(5) We will comment quickly

Thanks,

Kathy

From: Lewis, Caya (HHS/IOS)
Sent: Thursday, October 17, 2013 4:09 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: OHRP

Kathy,

It's good to be back.

(b)(5)

Talk to you soon,

Caya

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, October 17, 2013 3:56 PM
To: Lewis, Caya (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: OHRP

Hi Caya –

Was nice to hear your voice this morning at OS staff meeting.

As we get back to our usual work, I wanted to share with you a summary of our concerns about the OHRP proposal for development of new guidance for standard of care research. You will recall a round of emails about this before the shutdown. (b)(5)

(b)(5)

Proposal for Draft Guidance on Matters Related to the Protection of Human Subjects in Research Studying Standard of Care[1] Interventions

DRAFT 9/26/2013

(b)(5)

Carr, Sarah (NIH/OD) [E]

From: James, Carla (HHS/OASH) <Carla.James@hhs.gov>
Sent: Friday, September 20, 2013 3:51 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Will do.

Carla D. James

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Friday, September 20, 2013 3:51 PM
To: James, Carla (HHS/OASH)
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Sure and can you include schedulers as well as the NIH principals (the others I cc'd).

From: James, Carla (HHS/OASH) [mailto:Carla.James@hhs.gov]
Sent: Friday, September 20, 2013 3:48 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Thank you Sarah!! ☺ I will send out a confirmation soon.

Thanks again.

Carla D. James

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Friday, September 20, 2013 3:43 PM
To: James, Carla (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; Abel, Kathy (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]; Hardesty, Rebecca (NIH/OD) [C]; Plude, Denise (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Carla,

Friday the 27th from 12:30 to 2:00 will work. Here is the full NIH contingent:

Kathy Hudson
Amy Patterson
Stephanie Devaney
Sarah Carr

Sarah

From: James, Carla (HHS/OASH) [mailto:Carla.James@hhs.gov]
Sent: Friday, September 20, 2013 2:35 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Thank you!

Counselors Office
- Caya Lewis
- Jeremy Sharp

OASH
- Howard Koh
- Wanda Jones
- Diana Gianelli

OHRP
- Jerry Menikoff
- Ivor Pritchard
- Julie Kaneshiro
- Irene Stith-Coleman

FDA
- Sara Goldkind
- Patrick McNeilly
- Robert Nelson
- Abram Barth

OGC
- Peggy Dotzel
- Davis Horowitz

Carla D. James

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Friday, September 20, 2013 2:32 PM
To: James, Carla (HHS/OASH)
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Carla,

I'll know something soon.

Meanwhile, can you tell me who else will be attending?

Sarah

From: James, Carla (HHS/OASH) [mailto:Carla.James@hhs.gov]
Sent: Friday, September 20, 2013 12:59 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Sarah -

I am sorry, please disregard the last e-mail. By any chance can NIH be available on 9/27 from 12:30 – 2:00?

Thanks.

Carla D. James

From: James, Carla (HHS/OASH)
Sent: Friday, September 20, 2013 12:15 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Hi Sarah –

By any chance can NIH **please** be available on 9/27 from 11:00 – 2:00? Thank you.

Carla D. James

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Friday, September 20, 2013 12:17 AM
To: James, Carla (HHS/OASH)
Subject: Re: SUPPORT Public Meeting: HHS Meeting on Next Steps

Carla,

The only option that will work for NIH is Wed from 2:30-3:30.

Not sure yet who else besides Kathy Hudson will participate but I'll get back to you as soon as we know.

Sarah

From: James, Carla (HHS/OASH) [mailto:Carla.James@hhs.gov]
Sent: Thursday, September 19, 2013 05:18 PM Eastern Standard Time
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Thank you

Carla D. James

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Thursday, September 19, 2013 4:52 PM
To: James, Carla (HHS/OASH)
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

I'll get back to you, Carla.

From: James, Carla (HHS/OASH) [mailto:Carla.James@hhs.gov]
Sent: Thursday, September 19, 2013 4:51 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Hi Sarah –

Below are some possible times for September 25 and 27 that we are looking at for this meeting. Can you or someone else please provide me NIH participant's and their availabilities?

Thank you for your help.

Wed. 9/25
2:30-3:30pm
3:30-4:30pm

Fri. 9/27
9:30-10:30am
12:30-2:00pm

Carla D. James
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1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Tel: 240-453-8234
Fax: 240-453-6909
Main Line: 240-453-6900
Carla.James@hhs.gov

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Wednesday, September 18, 2013 3:29 PM
To: Kaneshiro, Julie A (HHS/OASH)

Cc: James, Carla (HHS/OASH)
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

I'll get back to you shortly with either a list of names or a coordinator.

From: Kaneshiro, Julie A (HHS/OASH)
Sent: Wednesday, September 18, 2013 3:24 PM
To: Carr, Sarah (NIH/OD) [E]
Cc: James, Carla (HHS/OASH)
Subject: SUPPORT Public Meeting: HHS Meeting on Next Steps

Hi Sarah,

The Secretary's Office would like OHRP to schedule a meeting sometime next week to discuss the development of guidance post the SUPPORT meeting. Participants in this meeting will include FDA, NIH, OGC, OS and OHRP.

Carla James will be contacting you about scheduling this meeting. Can you let us know who from NIH we should include? Would it be easier to coordinate schedules through you or someone else?

We will be trying to schedule this for some time next week, probably Wednesday or Friday.

Thanks so much!

Julie

Carr, Sarah (NIH/OD) [E]

From: Kaneshiro, Julie A (HHS/OASH)
Sent: Wednesday, September 18, 2013 3:30 PM
To: Carr, Sarah (NIH/OD) [E]
Cc: James, Carla (HHS/OASH)
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

Thanks, Sarah.

From: Carr, Sarah (NIH/OD) [E] [mailto:CarrS@OD.NIH.GOV]
Sent: Wednesday, September 18, 2013 3:29 PM
To: Kaneshiro, Julie A (HHS/OASH)
Cc: James, Carla (HHS/OASH)
Subject: RE: SUPPORT Public Meeting: HHS Meeting on Next Steps

I'll get back to you shortly with either a list of names or a coordinator.

From: Kaneshiro, Julie A (HHS/OASH)
Sent: Wednesday, September 18, 2013 3:24 PM
To: Carr, Sarah (NIH/OD) [E]
Cc: James, Carla (HHS/OASH)
Subject: SUPPORT Public Meeting: HHS Meeting on Next Steps

Hi Sarah,

The Secretary's Office would like OHRP to schedule a meeting sometime next week to discuss the development of guidance post the SUPPORT meeting. Participants in this meeting will include FDA, NIH, OGC, OS and OHRP.

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Thanks so much!

Julie

From:	Carr, Sarah (NIH/OD) [E]
To:	Hudson, Kathy (NIH/OD) [E]
Cc:	Patterson, Amy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]
Subject:	FW: Copy of letter to the Secretary regarding Transfusion of Prematures TOP Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically Intact Survival of Extremely Low Birth Weight Infants as Compared to Restrictive Strategy
Date:	Tuesday, September 17, 2013 5:06:32 PM
Attachments:	Sec"y Sign ltr Public Cit TOP 091013.docx InfoSheet.pdf FW Letter regarding the TOP trial.htm.htm 130822_Letter to Secretary Sebelius re TOP Trial_FINAL.pdf.pdf

Here it is.

-----Original Message-----
From: Borror, Kristina C (HHS/OASH)
Sent: Tuesday, September 17, 2013 1:41 PM
To: Carr, Sarah (NIH/OD) [E]
Subject: FW: Copy of letter to the Secretary regarding Transfusion of Prematures TOP Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically Intact Survival of Extremely Low Birth Weight Infants as Compared to Restrictive Strategy

Sarah:
I'm forwarding the attached letter to the Secretary complaining about an NIH-funded study in case you weren't aware of this. Attached also is a draft response to the letter which is in clearance downtown. OGC expects to suggest adding the following sentence:

(b)(5)

Let me know if you have any questions.
Kristina

-----Original Message-----
From: SWIFT, Administrator (HHS/OS)
Sent: Monday, August 26, 2013 2:25 PM
To: Borror, Kristina C (HHS/OASH)
Subject: Copy of letter to the Secretary regarding Transfusion of Prematures TOP Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically Intact Survival of Extremely Low Birth Weight Infants as Compared to Restrictive Strategy

SWIFT Info Copy of a Info Task

(Deadline:)

Instructions given to task recipients:

Response Directions:

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

August 22, 2013

The Honorable Kathleen Sebelius
Secretary
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

RE: Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy?

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to express deep concern regarding the recurrence of serious ethical lapses in another clinical trial involving extremely premature infants — the Transfusion of Prematures (TOP) Trial — that is being funded by the National Institutes of Health (NIH) and conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development's (NICHD's) Neonatal Research Network (NRN). These ethical lapses, particularly with respect to the consent process, closely parallel those described in our April 10, 2013, letter[1] and subsequent May 8, 2013, letter and in-depth report[2] regarding another NRN study — the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT). Unlike the SUPPORT study, in which concerns about serious ethical lapses were disclosed four years after subject enrollment was completed, the TOP trial investigators appear to be actively recruiting subjects at 15 different institutions (see Appendix). We therefore urge an immediate halt to the study due to the serious deficiencies in the consent forms and unresolved questions about the ethics of the study design.

[1] Carome MA, Wolfe SM. Letter to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT Study. April 10, 2013. http://www.citizen.org/documents/2111.pdf. Accessed August 21, 2013.
[2] Carome MA, Wolfe SM, Macklin R. Letter and report to Secretary of Health and Human Services Kathleen Sebelius regarding the SUPPORT study. May 8, 2013. http://www.citizen.org/documents/2124.pdf. Accessed August 21, 2013.

The TOP trial, interestingly subtitled "Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy," is designed to primarily determine which of two strategies for treating anemia with blood transfusions is more likely to result in death or neurologic injury in extremely premature infants who develop anemia (low red blood cell or hemoglobin levels, hemoglobin being a component of red blood cells that carries oxygen from the lungs to the other organs in the body). The projected enrollment for the TOP trial is 1,824 infants. These highly vulnerable infants are to be randomly assigned to one of two groups, irrespective of their individual medical needs. In one group, the infants are to be transfused whenever their blood hemoglobin levels fall below a relatively high threshold level (liberal transfusion group). In the second group, infants are to be transfused when their hemoglobin levels fall below a very low hemoglobin level (restrictive transfusion group). Under the protocol, transfusions may be given to either group in exceptional urgent or emergent circumstances, even if the protocol-specified hemoglobin thresholds have not been reached. Of note, the best available evidence, previously published by some of the TOP trial investigators themselves and extensively cited in the TOP trial protocol, suggests, overall — as does the study's subtitle — that the restrictive transfusion strategy is more likely to result in neurologic injury and other harms in extremely premature infants.

As in the SUPPORT study, the consent forms approved by the institutional review boards (IRBs) for the TOP trial — which, along with the complete TOP trial protocol, we obtained under a Freedom of Information Act request submitted to NIH — omit very important and material information regarding the purpose, nature, and risks of the experiment. Among the information not disclosed is the evidence from the aforementioned prior randomized trials suggesting that a restrictive transfusion threshold is more harmful than a liberal one. Furthermore, all of the consent forms include very misleading statements equating participation in the research with standard of care, and the majority of individual institutional consent forms indicate that the experimental interventions in the trial have no risk. As a result, the parents of potential TOP trial subjects are being denied the opportunity to make an informed decision about whether to enroll their infants in the research. It seems unlikely that any parent who fully understands the results of the prior clinical trials, as well as the true risks, purpose, and nature of the experiment, would be willing to enroll their premature infant in this study.

Additionally, and also as in the SUPPORT study, there are several unresolved serious ethical concerns regarding the design of the TOP trial and the adequacy of the IRB review of the research. In particular, we are very concerned about the lack of an appropriate control group that receives usual care (i.e., transfusions when needed based on individualized, patient-specific clinical factors) and the lack of a clear description of the pretrial standard transfusion practices at the NRN centers participating in the TOP trial. Given the former, adequate safety monitoring of the trial is not possible and as a result, risks to subjects are not minimized and reasonable in

relationship to any benefits of the research.[3] Given the latter, the IRBs that reviewed and approved the protocol: (a) would not have had sufficient information to understand the degree to which the experimental interventions deviate from the usual care at the NRN centers and the risks thereby posed by these deviations; and (b) could not determine whether risks to subjects are minimized and reasonable in relationship to any benefits of the research.

We therefore urge you to:

(1) Order an immediate halt to the TOP trial, if you have not already done so per our prior request for such action.

(2) Direct the Office of Human Research Protections (OHRP) to immediately open a compliance oversight investigation into the trial.

(3) Direct OHRP to develop a plan for contacting the parents of subjects already enrolled in the trial and providing them with a complete and accurate description of the risks, purpose, and nature of the research.

(4) Initiate an independent investigation of the Department of Health and Human Services (HHS) system for review and oversight of HHS-funded human subjects research to understand how the system failed so miserably in both the SUPPORT study and the TOP trial. This investigation should include an assessment of all entities within NIH and other HHS agencies that played a role in the review, approval, and funding and oversight of the SUPPORT study and TOP trial. In addition, given the widespread failures across multiple IRBs that reviewed and approved the SUPPORT study and TOP trial, HHS should determine what systemwide actions are needed to prevent such failures from recurring.

(5) Identify and suspend any similarly unethical research involving premature infants funded by NIH or any other HHS agency.

We provide below a more detailed review of our concerns.

[3] Minneci PC, Eichacker PQ, Danner RL, et al. The importance of usual care control groups for safety monitoring and validity during critical care research. *Intensive Care Med.* 2008;34:942-947.

I. Background

A. Prior randomized clinical trials testing liberal versus restrictive transfusion strategies in extremely premature infants

Anemia is very common in extremely premature infants due to many factors, including the need to draw multiple blood samples for various clinical tests and the relative impairment of the neonatal ability in producing new red blood cells.[4] Significant anemia can lead to inadequate delivery of oxygen to body organs, causing cardiac stress, apnea, brain injury, and other complications, including death in the most severe cases. To prevent such complications, the majority of extremely premature infants receive one or more blood transfusions.[5] Although transfusion of red blood cells is generally considered to be very safe, such treatment does carry possible risks, including:[6,7]

- Delays in the maturation of the immature infant's bone marrow and the ability of the baby to produce its own red blood cells;
- Volume overload and congestive heart failure;
- Transmission of certain infections, such Human Immunodeficiency virus (HIV) and Cytomegalovirus (CMV);
- Adverse effects on blood potassium, calcium, and glucose levels;
- Iron overload, which may increase the risk of chronic lung disease (bronchopulmonary dysplasia), retinopathy of prematurity (an eye disease in premature infants that can lead to blindness), or necrotizing enterocolitis; and
- Transfusion reactions.

Deciding when — at what level of anemia — to transfuse a premature infant involves: (a) balancing the risks of anemia and those of blood transfusions; and (b) considering numerous individual patient factors, including the following:[8,9,10]

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[4] Widness, JA. Pathophysiology of anemia during the neonatal period, including anemia of prematurity. *NeoReviews.* 2008;9(11):e520 -e525.
[5] Maier RF, Sonntag J, Walka MM et al. Changing practices of red blood cell transfusions in infants with birth weights less than 1000 g. *J Pediatr.* 2000;136(2):220-4.
[6] Ohls, R. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.
[7] Martin RJ, Fanaroff AA, Walsh MC. "The blood and hematopoietic system." *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant* 9th edition. Mosby 2011. P1303-1374. print
[8] Ohls, Robin. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.
[9] Guillen U, Cummings JJ, Bell EF, et al. International survey of transfusion practices for extremely premature infants. Semin Perinatol. 2012;36:244-247.

- Current level of anemia;
- Active bleeding or coagulopathy;
- The degree of supplementary oxygen required;
- Level of respiratory support (e.g., intubation, positive pressure ventilation, nasal cannula);
- Age of the baby;
- Reticulocyte count (count of new red blood cells);
- The need for medication to help the heart pump blood (inotropic support); and
- Major comorbidities, such as heart disease or sepsis.

Other factors sometimes taken into account that support transfusion include:[11,12]

- Lactic acidosis;
- Increasing episodes of apnea (stopping breathing);
- Persistent tachycardia (abnormally fast heart rate);
- Persistent tachypnea (fast breathing); and
- Poor weight gain.

Thus, decisions about when to transfuse premature infants are routinely based on a variety of individual patient-specific factors.

Results of two earlier, relatively large randomized clinical trials comparing liberal and restrictive experimental blood transfusion strategies in extremely premature infants were published between 2005 and 2009 in articles co-authored by some of the TOP trial investigators and are extensively cited by the TOP trial investigators in their protocol to justify their new study.[13] One was a single-center trial conducted at the University of Iowa involving 100 infants (the IOWA study[14,15]), and the other was a multicenter study conducted at 10 institutions in Canada, the U.S.,

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[10] Fanaro S. Blood transfusion in infants: techniques and adverse events. J Matern Fetal Neonatal Med. 2011 Oct;24 Suppl 1:47-9.
[11] Ohls, R. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.
[12] Fanaro S. Blood transfusion in infants: techniques and adverse events. J Matern Fetal Neonatal Med. 2011 Oct;24 Suppl 1:47-9.
[13] Kirplani H, Bell E, D'Angio C, et al. Transfusion of prematures (TOP) trial: does a liberal red blood cell transfusion strategy improve neurologically-intact survival of extremely-low-birth-weight infants as compared to a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. http://www.citizen.org/documents/2150a.pdf. Accessed August 20, 2013.
[14] Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics.* 2005;115(6):1685-91.
[15] Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr.* 2006 Sep;149(3):287-9.

and Australia known as the Premature Infants in Need of Transfusion Study (the PINT study[16,17]) involving 451 infants. The results of both studies combined suggest worse outcomes for the infants who were in the restrictive transfusion groups.

The IOWA study, which included 51 infants in the liberal transfusion group and 49 in the restrictive transfusion group, had the following findings:[18,19]

- Sixteen percent of infants in the restrictive transfusion group versus 2% in the liberal transfusion group died or had significant brain injury (defined as grade 4 intraventricular brain hemorrhage or periventricular leukomalacia, a condition seen in premature babies that involves death of brain tissue) ($p<0.05$).
- Infants in the restrictive transfusion group had statistically significantly greater and more severe episodes of apnea (periods when the infant stopped breathing) than the liberal transfusion group.
- Children in the restrictive transfusion group received approximately *nine-fold* more urgent or emergent rescue transfusions (on average per child) for "congestive heart failure … ascribed to anemia; acute hemorrhage and presumed hypovolemia; frequent severe apnea refractory to drug treatment … or request by a surgeon or anesthesiologist for preoperative transfusion" than those in the liberal transfusion group (17 in the restrictive transfusion group versus 2 in the liberal transfusion group, with an average number of transfusions per subject of 0.35 versus 0.04, respectively).[20]

In more recent unplanned follow-up neuroimaging[21] and developmental evaluations[22] of a subset of the IOWA study subjects, there was some indication that contrary to initial findings, the

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[16] Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr.* 2006 Sep;149(3):301-307.
[17] Whyte RK, Kirpalani H, Asztalos EV, et al. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. *Pediatrics.* 2009 Jan;123(1):207-13.

[18] Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics.* 2005;115(6):1685-91.
[19] Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr.* 2006 Sep;149(3):287-9.
[20] Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics.* 2005;115(6):1685-91
[21] Nopoulos PC, Conrad AL, Bell EF, Strauss RG, Widness JA, Magnotta VA, Zimmerman MB, Georgieff MK, Lindgren SD, Richman LC. Long-term outcome of brain structure in premature infants: effects of liberal vs restricted red blood cell transfusions. *Arch Pediatr Adolesc Med.* 2011 May;165(5):443-50.
[22] McCoy TE, Conrad AL, Richman LC, Lindgren SD, Nopoulos PC, Bell EF. Neurocognitive profiles of preterm infants randomly assigned to lower or higher hematocrit thresholds for transfusion. *Child Neuropsychol.* 2011;17(4):347-67.

restrictive transfusion group may have fared better with regard to long-term neurodevelopmental outcomes. However, as recognized in the TOP trial protocol and by others,[23] these follow-up studies are marred by substantial attrition (~44%), resulting in a high likelihood of bias, seriously compromising the validity and any generalizability of the follow-up studies. Of note, children who were enrolled in the follow-up studies had significantly greater mean hematocrits in infancy than those who were lost to follow-up (hematocrit 44 versus 37, p=<0.001), demonstrating that there could have been a selection bias in the follow-up studies. Thus, these two follow-up studies are at best uninformative and at worse misleading, and these results should be discounted when assessing the totality of available data from the randomized clinical trials.

The PINT study, which enrolled 223 infants in the restrictive transfusion group and 228 in the liberal transfusion group, demonstrated the following:

- More infants in the restrictive transfusion group experienced one or more of the following components of the composite primary endpoint before first discharge to home: death, severe eye disease (retinopathy of prematurity), lung disease (bronchopulmonary dysplasia), or brain injury, although results were not significant (74% in the restrictive group versus 70% in the liberal group, p=0.25)[24]
- In subjects followed for 18 to 21 months, death or neurodevelopmental impairment occurred in 45% of restrictive transfusion group subjects and 38% of liberal transfusion group subjects (p=0.09). The differences between the two study groups in mortality and the rates of neurological impairment outcomes (any neurological impairment, cerebral palsy, cognitive delay, severe visual impairment, and severe hearing impairment) were each less favorable for the restrictive transfusion group, but none were statistically significant.[25]
- Infants in the restrictive transfusion group received twice as many urgent or emergent rescue transfusions (on average per child) "in the event of shock, severe sepsis, coagulation defects, surgery, or for unanticipated emergencies" than those in the liberal transfusion group (173 in the restrictive transfusion group versus 87 in the liberal

[23] Venkatesh V, Khan R, Curley A, New H, Stanworth S. How we decide when a neonate needs a transfusion. *Br J Haematol.* 2013 Feb;160(4):421-33.
[24] Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr.* 2006 Sep;149(3):301-307.
[25] Whyte RK, Kirpalani H, Asztalos EV, Andersen C, Blajchman M, Heddle N, LaCorte M, Robertson CM, Clarke MC, Vincer MJ, Doyle LW, Roberts RS; PINTOS Study Group. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. *Pediatrics.* 2009 Jan;123(1):207-13.

transfusion group, with an average number of transfusions per subject of 0.78 versus 0.38, respectively).[26]

- In a post hoc analysis presented by TOP trial investigators, there was a significantly higher incidence of cognitive delay (defined as Mental Development Index <85) in the restrictive group (44.9% in the restrictive transfusion group versus 33 percent in the liberal transfusion group).[27]

Of these two prior randomized clinical trials, the PINT study should be given the most weight because it is multicenter and has a much larger subject enrollment. Nevertheless, data from both trials overall suggests that extremely premature infants fared worse under restrictive transfusion guidelines than under liberal transfusion guidelines.

Indeed, in a 2006 editorial following publication of the results of the IOWA and PINT studies, Dr. Edward Bell, the TOP trial vice chair, wrote the following:[28]

> The question remains of how far we can push the anemic preterm infant before transfusing him. Efforts to eliminate transfusions should be revisited in light of the **minimal benefits of restrictive transfusion practice** shown in these two trials and the **potentially major benefits of liberal transfusion practice** shown in the Iowa Trial. Perhaps the drive to eliminate transfusions by tolerating moderate to severe iatrogenic anemia should be halted until more information is available. **The advantage of fewer transfusions is small compared with the potential benefit of more liberal transfusions in protecting the brain.** [emphasis added]

B. Overview of the TOP trial[29]

The TOP trial is to be conducted by at least 19 NRN centers across the country. The infants to be enrolled are between 22 and 29 weeks gestational age, weigh less than 1 kilogram (2.2 pounds),

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[26] Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr*. 2006 Sep;149(3):301-307.

[27] Kirplani H, Bell E, D'Angio C, et al. Transfusion of prematures (TOP) trial: does a liberal red blood cell transfusion strategy improve neurologically-intact survival of extremely-low-birth-weight infants as compared to a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. http://www.citizen.org/documents/2150a.pdf. Accessed August 20, 2013.

[28] Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr.* 2006 Sep;149(3):287-9. PubMed PMID: 16939732.

[29] Kirplani H, Bell E, D'Angio C, et al. Transfusion of prematures (TOP) trial: does a liberal red blood cell transfusion strategy improve neurologically-intact survival of extremely-low-birth-weight infants as compared to a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. http://www.citizen.org/documents/2150a.pdf. Accessed August 20, 2013.

and are in their first 48 hours of life. As of July 19, 2013, 15 of 19 institutions within the NRN consortium are currently recruiting premature infants into the TOP trial, according to the entry for this trial at clinicaltrials.gov.[30]

Like the PINT and IOWA studies, infants enrolled in the TOP trial are to be randomly assigned to one of two transfusion groups, largely irrespective of their individual medical needs. The table below indicates the target hemoglobin levels at which infants are to be transfused and shows that babies in the restrictive transfusion group have to become much more anemic before they are transfused according to the protocol-specified criteria.

Hemoglobin Thresholds for Transfusion in the TOP Trial (All units in gm/dl)

TOP				
Postnatal Age	Restrictive		Liberal	
Days	Resp. Support	No Support	Resp. Support	No Support
1-7	11	10	13	12
8-14	10	8.5	12.5	11
>15	8.5	7	11	10

The specifically stated primary aim of the TOP trial is to examine whether the composite primary outcome of death or significant neurodevelopmental impairment (evidence of brain injury) at 22 to 26 months corrected age is less common among preterm infants who, by transfusion practice, are maintained at higher hemoglobin levels (i.e., managed according to a liberal transfusion threshold) than in infants with restrictive transfusion thresholds. Neurodevelopmental impairment is defined by cognitive delay (Mental Developmental Index <85), cerebral palsy, severe vision impairment, or severe hearing impairment.

Key stated short-term secondary outcome measures in the TOP trial include, among others:

- Survival to discharge without severe morbidity, defined as any of the following: bronchopulmonary dysplasia retinopathy of prematurity, or serious brain abnormality (grade 3 or 4 intraventricular hemorrhage, periventricular leukomalacia, or ventriculomegaly);
- Serious brain abnormality on cranial ultrasound examination;
- Number of transfusions and number of donor exposures by red blood cell donors or other blood products; and
- Episodes of necrotizing enterocolitis of Bell stage 2 or higher, and time to full-time feeds.

[30] Transfusion of prematures trial (TOP). http://clinicaltrials.gov/ct2/show/NCT01702805. Accessed August 21, 2013.

In discussing the basis for selecting the two sets of thresholds for the restrictive and liberal transfusion groups, the TOP trial investigators stated the following in their protocol:[31]

> We base our proposed transfusion thresholds on:
>
> i. The range of hemoglobin thresholds used clinically to guide transfusion decisions in the participating NICUs of the NICHD Neonatal Research Network;
>
> ii. A poll of the range of hemoglobin thresholds that would be acceptable to each neonatologist in an NRN site within the context of an RCT.
>
> The low threshold values reflect more common practice, so this is considered the "usual treatment" group. In this group, the transfusion thresholds are similar to those used for the restrictive group in both the PINT and Iowa studies. The highest threshold for the liberal transfusion group was the highest acceptable to neonatologists at the majority of NRN centers.

The TOP trial protocol provides no specific data regarding the survey of transfusion thresholds in the participating NRN NICUs, nor does it describe all of the specific clinical parameters that would alter the threshold for transfusion in individual patients under usual care at these institutions. In addition, the TOP trial investigators' statement that the low threshold values reflect more common practice at the NRN NICUs is somewhat surprising in light of the results of an international survey study that was co-authored by the chair and vice chair of the TOP trial (Dr. Haresh Kirpalani and Dr. Bell, respectively) and cited in the TOP trial protocol.[32] This international survey involved 1,018 neonatologists from 11 countries, 67 percent of whom were in the U.S. Most notably, the thresholds selected for the restrictive transfusion group in the TOP trial are at, or in some cases substantially lower than, the 25th percentile of the threshold used by the neonatologists who participated in the international survey.

The two experimental groups have the following two features that in combination cause the study interventions to deviate from the usual care for infants not enrolled in the research:

(1) The choice of transfusion thresholds at the extremes of current practice; and

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[31] Kirplani H, Bell E, D'Angio C, et al. Transfusion of prematures (TOP) trial: does a liberal red blood cell transfusion strategy improve neurologically-intact survival of extremely-low-birth-weight infants as compared to a restrictive strategy? Protocol Version 1.0; Final: October 8, 2012. http://www.citizen.org/documents/2150a.pdf. Accessed August 20, 2013.

[32] Guillen U, Cummings JJ, Bell EF, et al. International survey of transfusion practices for extremely premature infants. *Semin Perinatol.* 2012;36:244-247.

(2) Transfusion algorithms based on only two (age and respiratory support) of the many clinical factors that would otherwise be taken into account to varying degrees in the usual care setting. (Other factors routinely used to decide whether to transfuse an individual infant that are not considered under the experimental interventions include, among other things, oxygen requirement, reticulocyte count, degree of respiratory support, and the presence of tachycardia or tachypnea.[33])

As a result, some infants randomly assigned to the *liberal* transfusion group will be transfused at higher hemoglobin levels than they otherwise would if not enrolled in the research. On the other hand, some infants randomly assigned to the *restrictive* transfusion group either: (a) will be transfused at lower hemoglobin levels than they otherwise would if not enrolled in the research; or (b) will *not* receive transfusions at hemoglobin levels above the restrictive hemoglobin threshold when they otherwise would if not enrolled in the research.

The TOP trial investigators acknowledge that harm can come as the result of randomization to restrictive or liberal transfusion practices when the decision to transfuse is typically based on guidelines informed by multiple individual patient factors. The authors attempt to mitigate this potential harm by allowing clinicians to bypass the assigned clinical transfusion algorithm when an infant's condition warrants acute urgent or emergent rescue transfusion. However, similar rescue transfusion strategies did not eliminate the less favorable outcomes seen in the IOWA and PINT studies for subjects in the restrictive transfusion groups.

II. Serious Deficiencies of the IRB-Approved TOP Trial Consent Forms

Through a Freedom of Information Act request submitted to NIH, we obtained the consent forms that were approved by IRBs at 17 institutions participating in the TOP trial (see Appendix). Based on a review of the protocol and these IRB-approved consent forms, we have determined that the TOP trial has the same types of serious flaws in informed consent as in the SUPPORT study with respect to the disclosure of the risks, purpose, and nature of the research.

A. Reasonably foreseeable risks

HHS human subjects protection regulations at 45 CFR 46.116(a)(2) require that when seeking informed consent for research, investigators provide subjects or their legally authorized representatives (in the case of the TOP trial, the parents of the premature infants) with a description of any reasonably foreseeable risks.

[33] Ohls, Robin. Red blood cells transfusions in the newborn. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013. Last update: April 2013.

The TOP trial poses a number of reasonably foreseeable risks to subjects. The random assignment of the premature infants to one of two thresholds of hemoglobin levels that are at either the high end or low end of the "usual range" — independent of certain clinical factors that would normally be taken into account in making transfusion decisions as part of routine care of an individual infant — clearly has the potential to alter the care that the premature infants would otherwise receive as part of usual care if they are not enrolled in the trial.

For example, it is likely that some infants randomly assigned to the restrictive transfusion group will receive, overall, fewer transfusions than they would otherwise receive as part of usual care if they were not in the trial. As a result, particularly in light of the results of the IOWA and PINT studies, reasonably foreseeable risks of the research include possible increased risks of brain injury, impaired neurologic development, apnea, and even death. Infants in the restrictive group are also at increased risk of needing urgent or emergent rescue blood transfusions.

In contrast, it is likely that some infants randomly assigned to the liberal transfusion group, which is identified as the experimental group, will receive more transfusions, overall, than they would otherwise receive as part of usual care if they were not enrolled in the trial. Thus, reasonably foreseeable risks of the research include the potential increased risk of:[34,35]

- Delays in the maturation of the immature infant's bone marrow and the ability of the baby to produce its own red blood cells;
- Volume overload and congestive heart failure;
- Adverse effects on blood potassium, calcium, and glucose levels;
- Iron overload, which may increase the risk of chronic lung disease (bronchopulmonary dysplasia), retinopathy of prematurity (an eye disease in premature infants that can lead to blindness), or necrotizing enterocolitis;
- Transmission of certain infections, such HIV and CMV; and
- Transfusion reactions.

Moreover, the inclusion of death and neurologic injury as components of the composite primary endpoint for the study, combined with the investigators' acknowledged uncertainty regarding the impact of each of the two experimental transfusion strategies on these outcomes, also warrants inclusion of these events as reasonably foreseeable risks. Indeed, the main purpose of the study is to see which group will have more deaths or neurologic injury.

---

[34] Fanaro S. Blood transfusion in infants: techniques and adverse events. *J Matern Fetal Neonatal Med.* 2011 Oct;24 Suppl 1:47-9.

[35] Martin RJ, Fanaroff AA, Walsh MC. "The blood and hematopoietic system." *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant* 9th edition. Mosby 2011. P1303-1374. print

However, all of the 17 IRB-approved consent forms, to varying degrees, fail to adequately disclose these reasonably foreseeable risks. Based on our analysis of the 17 consent forms, key observations regarding the discussion of the research risks include the following:

(1) Only one consent form indicates that there may be an increased risk of death or disability associated with the two research interventions.

(2) Fifteen consent forms conflate the potential risk of the research with the risks of routine medical care outside the research context by stating the following or something very similar:[36]

> The risks associated with this study are exactly the same risks that exist in current medical practice and in blood transfusion therapy.

(3) Four consent forms include the following misleading statement or a very similar one:[37]

> This study does not carry any additional risk to your baby if you choose to take part.

(4) One consent form includes the following misinformation:[38]

> There are no known risks at this time to participation in this study.

(5) Twelve consent forms indicate that giving too much blood may delay blood production by the infants' own bone marrow and that not giving enough blood may result in the infants not having enough hemoglobin to carry oxygen around the body.[39] However, these consent forms proceed to declare that such problems will not occur in this trial because the study avoids these extremes by transfusing within the ranges of hemoglobin level routinely used by doctors.

(6) None of the consent forms describe the likely increased need for infants assigned to the restrictive transfusion group to receive more of urgent or emergent rescue transfusions for "clinical need," as was clearly shown in the PINT and IOWA studies.[40]

---

[36] *Ibid*.
[37] IRB-approved consent forms for the TOP trial. http://www.citizen.org/documents/2150b.pdf. Accessed August 21, 2013.
[38] *Ibid*.
[39] *Ibid*.
[40] *Ibid*.

(7) Only two consent forms come close to presenting an appropriate description of the risks by presenting a more extensive, albeit incomplete, description of the different risk profiles for each experimental group. The following is an excerpt from of these:[41]

> Possible risks with transfusions done to keep your baby's hemoglobin at a higher level include:
>
> If your baby is randomized to the high group it may result not only in more blood transfusions, but the babies may take longer to mature their own bone marrow to produce their own blood. Increased administration of fluids may delay closure of the PDA. An increased number of transfusions may result in a higher amount of iron in your baby's body. Too much iron may increase the risk of chronic lung disease (also called BPD), retinopathy of prematurity (an eye problem in premature infants) or necrotizing enterocolitis … .
>
> Possible risks with transfusions done to keep your baby's hemoglobin at a lower level include:
>
> If your baby is randomized to the low group, they will receive fewer transfusions. A baby with a low hemoglobin level could lead to the baby not having enough hemoglobin to carry oxygen around the body. The frequency of apnea of prematurity may be increased, and weight gain may be slower.

B. Purpose of the research

HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent for research, investigators provide subjects or their legally authorized representatives with an explanation of the purposes of the research.

Given the primary aim of the study, the TOP trial investigators should be informing parents of potential subjects that the main purpose of the research is to determine whether extremely premature infants are more or less likely to die, or more or less likely to develop neurologic impairment (brain damage), if they are managed with a liberal versus restrictive blood transfusion strategy.

While the title of the study (Transfusion of Prematures (TOP) Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically-Intact Survival of Extremely-Low-Birth-Weight Infants as Compared to Restrictive Strategy?) — which appears on 15 of the IRB-

[41] *Ibid*.

approved consent forms[42] — reflects the primary study aim, most parents of prospective subjects are unlikely to derive an understanding of the primary purpose of this trial from the complex language used in the title. A review of specific explanations of the purpose of the research in 17 IRB-approved consent forms reveals that only two include reference to assessing mortality and only five mention an assessment of neurodevelopment or development.[43] Thus, the majority of IRB-approved consent forms fail to clearly explain the most important purposes of the research.

Finally, in discussing the purpose of the study, all of the IRB-approved consent forms included a statement similar to the following:[44]

> When the hemoglobin falls below a certain level, doctors will transfuse the baby. However, we know that some doctors tend to use a higher level of hemoglobin and some doctors tend to use a lower level of hemoglobin. The reason for this is that we do not know which level of hemoglobin is better. This study aims to help us find out when we should best transfuse babies.

This statement incorrectly implies that nothing is known about what hemoglobin threshold to use when deciding when to transfuse premature infants. None of the consent forms discuss the results of the major randomized studies prior to the TOP trial (the PINT and IOWA studies) which, as discussed above, suggest overall that there are worse outcomes with a restrictive transfusion strategy than a liberal one. Nor do the consent forms explain that the TOP trial investigators, as implied in the title of the study, are trying to definitively prove whether a liberal strategy is indeed safer than a restrictive one.

C. Description of the research interventions

HHS regulations at 45 CFR 46.116(a)(1) require that when seeking informed consent, investigators provide subjects or their legally authorized representatives with a description of the procedures to be followed and identification of any procedures that are experimental.

In numerous ways and to varying degrees, all of the IRB-approved consent forms for the TOP trial fail to adequately describe the research procedures, identify the procedures that are experimental, and distinguish those procedures from the usual care the infants would receive if not enrolled in the research. Both study groups receive experimental interventions that are intended to alter the timing of blood transfusion decisions in comparison to transfusion decisions that would be made if they were not enrolled in the research. Not only do most of the consent

[42] *Ibid*.
[43] *Ibid*.
[44] *Ibid*.

forms fail to clearly identify these experimental procedures and how they differ from usual care, but they clearly misrepresent the nature of the study interventions by stating that the two thresholds for transfusing infants enrolled in the trial are within the range of normal or usual care given to infants not in the research. In particular, we note the following:

(1) As previously discussed, as part of routine care outside the research context, the hemoglobin level at which a particular premature infant would be transfused is routinely based on consideration of many individual patient factors, only some of which are taken into consideration in the experimental algorithms for the liberal and restrictive transfusion groups. Note also that an experimental algorithm based in part on a poll of hemoglobin thresholds that would be acceptable to neonatologists *in the context of a randomized clinical trial* is not the same as what the hemoglobin thresholds for blood transfusion would be in usual care outside of a clinical trial. None of the consent forms clearly describe how the research interventions deviate from the usual individualization of transfusion care in extremely premature infants not enrolled in the study.[45]

(2) Only two of the 17 IRB-approved consent forms identified the restrictive group as being the usual approach for infants not enrolled in the research at that institution.[46] None of the other consent forms explained how the thresholds used for the two experimental groups compared to those used at the institution where the infant would be hospitalized if not enrolled in the research.

(3) Seven consent forms included the following misleading statement or one very similar to it:[47]

> This study does not alter the routine care of your baby.

(4) Sixteen consent forms included the following uninformative and misleading statement that blurred the distinction between the two research interventions being tested and the individualized transfusion decisions that would occur for infants not enrolled in the research:[48]

> Both of these [hemoglobin threshold] levels [for determining when to transfuse blood] are in the usual range used by doctors in the NICU.

[45] *Ibid*.
[46] *Ibid*.
[47] *Ibid*.
[48] *Ibid*.

Given the nature of the TOP trial protocol, these deficiencies in the consent forms approved by the IRBs at 17 major academic medical centers regarding the research risks, purpose, and experimental procedures are disturbing, but perhaps not surprising, given what we now know about what occurred in the SUPPORT study, involving many of the same institutions and investigators. Like the SUPPORT study, such egregious consent deficiencies deprive parents of the opportunity to make an informed decision about whether to enroll their infants in the research and thus represent a serious violation of research ethics. Finally, it seems unlikely that any parent who fully understands the results of the prior clinical trials, as well as the true risks, purpose, and nature of the experiment, would be willing to enroll their premature infant in this study.

III. Ethical Concerns Regarding the Design of the TOP Trial

In addition to the clear deficiencies regarding the informed-consent process for the SUPPORT study, we have significant ethical concerns about the design of the study. In particular, it appears that the study as designed failed to satisfy the requirements of the following provisions of the HHS human subjects protection regulations:

> (1) 45 C.F.R. 46.111(a)(1), which requires that as a condition of approval, the IRB must determine that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; and
>
> (2) 45 C.F.R. 46.111(a)(2), which requires that as a condition of approval, the IRB must determine that risks to subjects are reasonable in relationship to any anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

While there are many features of the protocol that raise ethical concerns, we describe two primary features below.

A. Lack of a control group

The TOP trial involves extremely premature infants who are critically ill, have a high baseline mortality rate, and require customized neonatal intensive care unit management. As discussed above, as part of routine care for such infants, decisions regarding the level of hemoglobin at which to transfuse blood would be individualized, based on multiple clinical factors.

The trial involves randomization to two experimental groups in which a fixed low or high hemoglobin threshold is used to determine when to transfuse blood, without taking into account some of the many factors that would be considered in such blood transfusion decisions. However, the trial lacks a control group receiving usual individualized care. Through randomization, the care of subjects will be changed from the usual care — individualized transfusion management provided to infants not enrolled in the study — to one of two experimental fixed target levels of transfusion thresholds, independent of perceived clinical need or an individualized assessment of risks and benefits. Without a control group involving individualized, usual care, adequate safety monitoring cannot be conducted by the data safety

and monitoring committee. Subjects in both experimental groups may experience an increased incidence of one or more adverse outcomes, including death, because of harmful misalignments. Yet these may go undetected without an appropriate usual care control group.[49]

Therefore, without an appropriate usual care control group, risks to subjects are not minimized, nor are they reasonable in relation to the anticipated benefits to the subjects or the knowledge to be gained.

B. Insufficient information on usual care

We are also concerned that the IRBs that reviewed the TOP trial were not provided with sufficient information to make the findings required under 45 CFR 46.111(a)(1) and (2). In particular, the TOP trial protocol lacks a robust, detailed explanation of the usual care regarding transfusion decisions in extremely premature infants at each of the participating NRN medical centers.

As noted above, the protocol indicates that the transfusion algorithm for triggering a transfusion in each experimental group was based on the range of hemoglobin thresholds used clinically to guide transfusion decisions at the participating NRN NICUs. But the TOP trial protocol only reports that the low threshold values reflect more common practice but otherwise provides no details about the survey of transfusion practices at NRN NICUs that apparently was conducted prior to development of the protocol. It is unclear whether the statement that the "low threshold values reflect more common practice" means that: (a) between the high and low transfusion thresholds, the low transfusion threshold is more common, or (b) the low transfusion threshold is the most common across the NRN centers. Knowing whether (a) or (b) is true is critical to understanding the degree to which the experimental interventions deviate from the usual care at the NRN centers and the risks thereby posed by these deviations.

To fully assess the risks of the trial and to fully understand how the experimental interventions would alter transfusion management of the subjects in each study group in comparison to usual care, the IRBs would need much greater detail about the results of the survey of usual transfusion thresholds across the NRN NICUs. This should include individual data for each center and summary data for all centers that include the range, mean, median, and interquartile range. The IRBs would also need a detailed description of all the clinical factors that are taken into account when determining when to transfuse an individual infant. It is very concerning that such important detailed information is lacking from the protocol. Without this information, determinations regarding whether the TOP trial satisfies the requirements of HHS regulations at 45 CFR 46.111(a)(1) and (2) cannot be made.

[49] Minneci PC, Eichacker PQ, Danner RL, et al. The importance of usual care control groups for safety monitoring and validity during critical care research. *Intensive Care Med.* 2008;34:942-947.

IV. Conclusions and Requested Actions

As in the SUPPORT study, the IRB-approved consent forms for the TOP trial omit very important and material information regarding the purpose, nature, and risks of the experiment. Furthermore, the consent forms include very misleading statements equating the participation in the research with standard of care, and the majority indicate that the experimental interventions in the trial have no risk. As a result, the parents of potential TOP trial subjects have been and are still being denied the opportunity to make an informed decision about whether to enroll their infants in the research.

There are also unresolved serious ethical concerns regarding the design of the TOP trial and whether the research satisfies the requirements of the HHS human subjects protection regulations at 45 C.F.R. 46.111(a)(1) and (2).

We therefore urge you to:

(1) Order an immediate halt to the TOP trial, if you have not already done so per our prior request for such action.

(2) Direct OHRP to open a compliance oversight investigation into the trial.

(3) Direct OHRP to develop a plan for contacting the parents of subjects already enrolled in the trial and providing them with a complete and accurate description of the risks, purpose, and nature of the research.

(4) Initiate an independent investigation of the HHS system for review and oversight of HHS-funded human subjects research to understand how the system failed so miserably in both the SUPPORT study and the TOP trial. This investigation should include an assessment of all entities within NIH and other HHS agencies that played a role in the review, approval, and funding of the SUPPORT study and TOP trial. In addition, given the widespread failures across multiple IRBs that reviewed and approved the SUPPORT study and TOP trial, HHS should determine what systemwide actions are needed to prevent such failures from recurring.

(5) Identify and suspend any similarly unethical research involving premature infants funded by NIH or any other HHS agency.

Thank you for your urgent attention to these matters. Please contact us if you have any questions or require any additional information.

Sincerely,

Gregory P. Weaver, M.D., M.P.H.
General Preventive Medicine Resident
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Founder, Senior Adviser
Public Citizen's Health Research Group

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group

cc: Dr. Francis Collins, Director, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development
Dr. Howard K. Koh, Assistant Secretary for Health, HHS
Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borror, Director, Division of Compliance Oversight, OHRP

APPENDIX: Institutions Participating in the TOP Trial

Brown University, Women & Infants Hospital of Rhode Island*§
Case Western Reserve University, Rainbow Babies and Children's Hospital*§
Children's Mercy Hospital*§
Cincinnati Children's Medical Center*§
Duke University Health System*§
Emory University*§
Indiana University*§
Research Institute at Nationwide Children's Hospital*§
Stanford University§
University of Alabama at Birmingham
University of Buffalo§
University of California, Los Angeles*§
University of Iowa*§
University of North Carolina at Chapel Hill§
University of New Mexico*§
University of Pennsylvania, Children's Hospital of Philadelphia*§
University of Rochester*§
University of Texas Health Science Center, Houston
University of Texas Southwestern Medical Center at Dallas*
Wayne State University*§

*Institutions actively recruiting as of July 19, 2013

§Institutions with IRB- approved consent forms released by NIH in response to a Freedom of Information Act request

From: Koh, Howard (HHS/OASH)
Sent: Thursday, August 22, 2013 4:27 PM
To: East, Janet (HHS/OASH)
Subject: FW: Letter regarding the TOP trial
Attachments: 130822_Letter to Secretary Sebelius re TOP Trial_FINAL.pdf

---

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Thursday, August 22, 2013 9:54 AM
To: Sebelius, Kathleen (HHS/OS)
Cc: Collins, Francis (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Menikoff, Jerry (HHS/OASH); Borror, Kristina C (HHS/OASH); Koh, Howard (HHS/OASH)
Subject: Letter regarding the TOP trial

Dear Secretary Sebelius:

Attached please find a letter from Public Citizen's Health Research Group regarding the lack of informed consent for another Neonatal Research Network clinical trial involving extremely premature infants: the TOP trial. The original hardcopy of our letter will follow by regular mail.

Thank you for your attention to this important matter.

Sincerely,

Michael A. Carome, M.D.
Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

Office of the Assistant Secretary for Health

Information Copy

Doc ID:	08232013B001	*Date Due:*	
Corr. From:	Michael Carome, et al.	*Task Date:*	
On Behalf Of:			
Date on Letter:	8/22/2013	*Date Inc Rec'd:*	8/23/2013

Subject: Copy of letter to the Secretary regarding Transfusion of Prematures TOP Trial: Does a Liberal Red Blood Cell Transfusion Strategy Improve Neurologically Intact Survival of Extremely Low Birth Weight Infants as Compared to Restrictive Strategy

Synopsis:

Primary Issues: None

Action Office: DCO

Info Copies: Odwazny, Laura (HHS/OGC); Bradley, Ann (HHS/OASH); Summers, Elyse (HHS/OASH); Kaneshiro, Julie A (HHS/OASH); StithColeman, Irene E (HHS/OASH); Pritchard, Ivor A (HHS/OASH); Lin, Melody (HHS/OASH); Menikoff, Jerry (HHS/OASH); Banks-Shields, Marinna (HHS/OASH); Buchanan, Lisa (HHS/OASH); Borror, Kristina C (HHS/OASH); OD; DPA; DED

Action Required: Info Only

Analyst: Toni Goodwin

Instructions: None

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From:	Burklow, John (NIH/OD) [E]
To:	Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Rockey, Sally (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc:	Wood, Gretchen (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; Alexander, Rashada (NIH/OD) [E]; Tatem, Anne (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Childress, Kerri (NIH/NICHD) [E]; Rowe, Mona (NIH/NICHD) [E]; Myles, Renate (NIH/OD) [E]; Jackson, Calvin (NIH/OD) [E]; Fine, Amanda (NIH/OD) [E]
Subject:	FW: AP: Preemie study sparks debate: How much should patients know about risks of research
Date:	Thursday, August 29, 2013 9:17:13 AM
Attachments:	image003.png

FYI

John Burklow
Associate Director for Communications and Public Liaison
National Institutes of Health
Building 1, Room 344
(301) 496-4461 (phone)
(301) 496-0017 (fax)
burklowj@od.nih.gov

png-800

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

From: Sye, Tait (OS/ASPA)
Sent: Thursday, August 29, 2013 8:59 AM
To: Broido, Tara (HHS/OASH); Lewis, Caya (HHS/IOS); Lee, Noelle C. (HHS/IOS); Gianelli, Diane M (OASH); Burklow, John (NIH/OD) [E]; Salcido, Dori (HHS/ASPA); Myles, Renate (NIH/OD) [E]; Bradley, Ann (HHS/OASH); Horowitz, David (HHS/OGC); Baldauf, Sarah (OS/ASPA)
Subject: AP: Preemie study sparks debate: How much should patients know about risks of research

Here is AP story on the public meeting. Didn't make it into the clips. Will include it in tomorrow's. No mention of the press conference.

Actually does a very good job of explaining the issues.

***

AP: Preemie study sparks debate: How much should patients know about risks of research

By LAURAN NEERGAARD AP Medical Writer
August 29, 2013 - 3:23 am EDT

http://www.therepublic.com/view/story/f5d99a77e7064ef7b6c88e74e0b4fd7f/US-MED--HealthBeat-Research-Risks

WASHINGTON — Dagen Pratt's parents enrolled their tiny premature baby in a study of oxygen treatment believing she'd get the best possible care. They didn't understand it was an experiment to test what dose works best. No one mentioned any risks.

Now 6, Dagen struggles with cerebral palsy, and they wonder: Is that long-ago study to blame?

"Tell me that the Support study did not hurt Dagen in any way," her father, Shawn Pratt, challenged a government panel on Wednesday as his daughter, dressed in a bright sundress, stood quietly by.

A major controversy has erupted over what sounds like a straightforward question: How much should patients be told about the potential risks before they're enrolled in certain kinds of medical research?

The issue isn't about how to study a brand-new, unapproved therapy. All sides agree that those studies must fully inform participants that there's no guarantee the experiment will work, or even be safe.

Instead, the debate is about one of modern medicine's dirty little secrets: Doctors frequently prescribe one treatment over another without any evidence to know which option works best. There's no requirement that they tell their patients when they're essentially making an educated guess, or that they detail the pros and cons of each choice.

Researchers are supposed to outline all the risks when they study which commonly used option is best. But could that mislead patients into thinking research is riskier than their own doctor's best guess?

Federal health officials put that question to the public Wednesday, as they debate how strictly to regulate this type of research — a debate sparked by that study of premature babies who included Dagen Pratt of Kingwood, West Virginia

The tiniest preemies face serious risks, including death and disabilities.

Oxygen has been a mainstay of treating them, but doctors didn't know just how much to use. Too much causes a kind of blindness called retinopathy of prematurity. Too little can cause neurologic damage, even death. So hospitals used a range of oxygen, with some doctors opting for the high end and some for the low.

The Support study, conducted between 2005 and 2009, aimed to settle which end of that range was the best dose. It randomly assigned about 1,300 preemies at 23 hospitals to a lower or higher oxygen dose. To researchers' surprise, slightly more babies who got the lower dose died, a finding that has led to new standards for the care of preemies.

The problem: A government watchdog agency last spring ruled that researchers violated federal regulations that required them to spell out the risks of the study for parents. Nowhere in the consent forms that parents had to sign was death mentioned.

"This was a very, very important study to do," Dr. Jerry Menikoff, head of the Office for Human Research Protections, stressed Wednesday. "All we were asking for," he added, "is a couple of sentences to say there were risks."

He agreed with consumer advocates that a similar study in New Zealand phrased the issue more appropriately, saying the question is whether the lower dose "is safe and effective in reducing serious vision and lung problems without increasing mortality or neurodevelopmental disability."

But critics, including the head of the National Institutes of Health, argued that back in 2005, doctors didn't think the lower dose really posed a survival risk — the question was more about which dose did a good-enough job at saving their vision.

In fact, preemies who didn't enroll in the study — and got whatever range of oxygen their doctors deemed best — turned out to have a higher risk of death, said NIH Deputy Director Kathy Hudson.

Dr. John Lantos, a bioethicist at Children's Mercy Hospital in Kansas City, Missouri, knows that firsthand. His twin grandsons were born during the Support study but weren't given an opportunity to enroll. One died soon after birth. The other today is thriving but suffered severe retinopathy and has poor vision.

"Nonvalidated therapy is often more dangerous than careful research," Lantos said, adding that the consent forms should make that clear as well. "Doctors just hate to say they don't know something. When they do say it, we should listen."

While the experts debated how to explain research risks, two families who traveled to Washington for the unusual meeting outlined a bigger hurdle: Reeling from the stress of having a vulnerable preemie, they simply didn't understand that they were participating in an experiment. And they still haven't been told what dose of oxygen their children received, and it's impossible to say whether lingering health problems are a consequence of the study or of being extremely premature.

Yet, they now wish they hadn't participated.

"I unknowingly placed my son in harm's way," said Sharissa Cook of Attalla, Alabama, who wonders if vision problems experienced by her 6-year-old, Dreshan Collins, were caused by the study or from weighing less than 2 pounds at birth. "The only thing a mother wants is for her baby to be well."

Dagen's mother, Carrie, was more blunt with reporters: "Why is omitting information not considered lying?" she said. "We were told they would give her the best care every day."

Gordon, Valery (NIH/OD) [E]

From: Carr, Sarah (NIH/OD) [E]
Sent: Saturday, August 10, 2013 2:47 PM
To: Gordon, Valery (NIH/OD) [E]
Subject: FW: SUPPORT Comments FW: Comments Submitted in Docket as of 8/8/2013
Attachments: Presenters Comments Submitted into Docket as of 8August2013[1].pdf

Valery, how should we proceed? Could Khair do a summary table of some kind and should we have Denise make binders?

From: Patterson, Amy (NIH/OD) [E]
Sent: Friday, August 09, 2013 5:11 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: SUPPORT Comments FW: Comments Submitted in Docket as of 8/8/2013

Hi Kathy,
Here are the comments submitted to OHRP in advance of the HHS meeting on the SUPPORT study issues. OHRP staff says the planning meeting is not yet on the books and will include only HHS officials (you, Rob Temple (FDA), Jerry, Caya, and other HHS leadership). The purpose of the meeting will be to figure out how to organize the commenters/meeting segments etc. Meanwhile, we are reviewing the comments.
Amy

From: StithColeman, Irene E (HHS/OASH)
Sent: Friday, August 09, 2013 3:35 PM
To: Patterson, Amy (NIH/OD) [E]
Subject: Comments Submitted in Docket as of 8/8/2013

Hi Amy,

Attached are the comments submitted in the Docket by presenters as of August 8, 2013.

Irene

Patterson, Amy (NIH/OD) [E]

From: StithColeman, Irene E (HHS/OASH)
Sent: Friday, August 09, 2013 3:51 PM
To: Patterson, Amy (NIH/OD) [E]
Subject: RE: Comments Submitted in Docket as of 8/8/2013
Attachments: Presenters Comments Submitted into Docket as of 8August2013[1].pdf

Let me know if you do not get the attachment.

Irene

From: StithColeman, Irene E (HHS/OASH)
Sent: Friday, August 09, 2013 3:35 PM
To: Patterson, Amy (NIH/OD) [E]
Subject: Comments Submitted in Docket as of 8/8/2013

Hi Amy,

Attached are the comments submitted in the Docket by presenters as of August 8, 2013.

Irene

PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 07, 2013
Status: Posted
Posted: August 08, 2013
Tracking No. 1jx-86wi-l1ar
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0015
Comment on FR Doc # 2013-15160

Submitter Information

Name: George Annas
Address: 02118
Email: annasgj@bu.edu

General Comment

See attached file(s)

Attachments

OHRP SOC Signed

Boston University School of Public Health
Department of Health Law, Bioethics & Human Rights

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BOSTON UNIVERSITY

August 7, 2013

Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Comments for HHS Public Meeting submitted electronically at www.regulations.gov

RE: **Docket HHS-OPHS-2013-0004,** Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions (78 FR 38343)

The following comments are in response to the notice published by the Department of Health and Human Services "requesting input regarding how an Institutional Review Board should assess the risks of research involving randomization to one or more standard of care interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process." 78 FR 38343 (June 26, 2013)

Others will address this issue from the point of view of investigators and research institutions. Our focus is on protecting the rights and welfare of research subjects and we will comment on the questions from the perspective of potential subjects.[1] Because of the overlapping nature of the questions, some points will be made more than once.

Before responding directly to the questions it should be noted that "risk" is not limited to the chance of physical or psychological harm. Risk includes the failure to respect subjects as persons which requires acknowledging that they are being asked to provide an important service

[1] Our use of the term "subject" includes individuals who will undergo the research interventions themselves and surrogate decision makers, such as parents, who are empowered to enroll others in research.

to the larger society—participating in research not for their current benefit, but for the future benefit of the community. This is the essential difference between clinical interventions and research interventions. Asking a person to become a research subject without making clear to the potential subject the purpose of the research, how research subjects will be treated differently from patients, and the potential risks of the research, is exploitative.

In addition, "risk" should not to be considered solely as the chance of harm to the *group* of potential research subjects. Risk means assessing the potential harms to each *individual* research subject. The ethical and legal obligation is to obtain informed and voluntary consent from every *individual* research subject. It is for this reason that we suggest it is essential that the questions the Department has presented be addressed from the perspective of the potential individual subjects. The very purpose of informed consent is to ensure the respectful treatment of individuals – not to protect researchers or institutions, or to further the interests of researchers, research institutions or sponsors.

We also wish to note at the outset that there is nothing exceptional about "standard of care" research that requires that it be treated any differently from any other form of research with human subjects. Indeed, there is nothing special about the concept of standard of care itself. Standard of care is simply a term that describes what doctors tend to do in certain circumstances. It is a description rather than a technical, scientific or medical concept. Standards of care come from a variety of sources and serve a variety of purposes. There is, for example, no entity that creates "the standard of care" or that controls how physicians may exercise their broad discretion to make reasonable treatment decisions with their patients. Standards of care can be derived from expert consensus panels and can be based on definitive scientific research. These are often referred to as "practice guidelines" rather than as definitive

standards. [2] But standards of care also come from what physicians learn at non-peer reviewed conference presentations, pharmaceutical company advertising and sales techniques, the non-validated practices of "experts" in their fields, the habits learned in training, and other informal sources.[3] For those who argue that doctors practice "defensive medicine" to protect themselves from lawsuits, standards of care are created to protect doctors from lawsuits, and not to protect patients from harm. Given all of this, there should be no special category for so-called standard of care research. Rather, every research protocol must be evaluated individually to determine if human beings are being appropriately used as research subjects to further scientific knowledge. One essential criterion for "appropriate use" is that all research subjects are informed of the fact that they will not be treated by their physician as they might be if they were patients rather than research subjects.

How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?

An IRB must consider the fact that subjects in this type of research may not receive what their own physicians consider to be the best care based on the physician's knowledge and experience. Indeed, subjects may not receive what a majority of physicians believe is the most effective or safest treatment – a bona fide question about which treatment is "best" does not require an even split in the medical community. Specifically, the subjects should be aware of the fact that the care that they will receive as research subjects will be determined randomly following a protocol created by someone other than their physician, and not based on their physician's best judgment. The fact that their physician's best judgment may ultimately not be proven to provide

[2] For a discussion of the problems inherent even in the explicit medical guideline-making process see: Sniderman, AD, and Furburg, CD, Why Guideline Making Requires Reform, *JAMA* 2009;301: 429-431.

[3] For a discussion of the non-medical or scientific pressures to adopt new practices as standard of care see: Linton , AL, Naylor, D, Organized Medicine and the Assessment of Technology: Lessons from Ontario, *N Engl J Med* 1990; 323: 1463-1467.

the best treatment does not detract from the fact that, unlike researchers whose primary interest is in gaining knowledge to benefit others, a physician is required to exercise individual professional judgment for the benefit of his or her patient. When patients are randomized they become subjects who no longer have a physician who is solely concerned with their best interest. The change in roles from physician to researcher and from patient to subject are especially important for subjects to understand when the person they sought treatment from will be "blinded," and therefore not able to receive information about the subject that could be clinically significant to a treating physician.

What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, or reasonably foreseeable and therefore required to be disclosed to subjects?

As we previously noted, when research subjects are randomized to determine which type of care they will receive, they are no longer receiving care based on the best judgments of an individual physician whose sole interest is the welfare of the patient. The consequences of this must always to be considered a risk of such research. Furthermore, subjects need to be informed that the treatment they would ordinarily receive for their condition at the institution from where they sought care will not be provided to at least half of the subjects because they will be randomized to receive another treatment. Assuming there is a reason to believe that one intervention is superior to another intervention, which is the very justification for this type of research, potential subjects need to be informed that if it turns out that the care usually offered at their institution is superior to the comparative intervention, that 50% of them will not receive this better care. On the other hand, if it turns out that the treatment they would have received if they were not in the research project is inferior to the alternative; research subjects can be informed that, while it is not the purpose of enrolling them in the research study, they could benefit from

being in the research. But it is essential that the potential risks and potential benefits be clearly described to potential research subjects who are the only ones who are entitled to weigh the risks and benefits in determining whether or not they want to become research subjects.

How should randomization be considered in research studying one or more interventions within the standard of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk? Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?

Randomization *procedures* themselves do not present a risk. Flipping a coin is risk free as long as no consequences follow from the outcome of the flip. Randomization is extremely risky, however, if a life or death decision is determined by a coin flip. Determining which medical treatment a person receives as a result of a coin flip always presents the risk of exploitation of research subjects. For example, there was a substantial controversy regarding the comparative risks and benefit of radical mastectomy and segmental mastectomy. In the 1980's both were used as "standard of care" by different surgeons. To resolve the controversy a randomized controlled clinical study was conducted in which women with breast cancer were randomly selected for one treatment or the other.[4] It is hard to imagine that anyone would seriously argue that this is low risk research because both treatments were used by some practitioners as standard treatments, or that the potential subjects would not need to be informed of the potential risks and benefits of each treatment before they consented to be randomized.

When people are ill they seek care from physicians whose sole goal should be to provide care designed to benefit them. Randomization deprives people of this special doctor-patient fiduciary relationship. By definition researchers do not have the special fiduciary obligation which is

[4] Fisher, B et.al, Five-Year Results of a Randomized Clinical Trial Comparing Total Mastectomy and Segmental Mastectomy with or without Radiation in the Treatment of Breast Cancer, *N Engl J Med* 1985; 312: 665-673.

defined as the obligation of the physician to use the best interests of the patient as the sole guide to care. Unlike treating physicians, a researcher's primary goal is to create new knowledge to benefit others. However noble or important this undertaking may be, it does not change the fact that researchers have a different relationship to their research subjects than physicians have to their patients. It is absolutely essential that potential research subjects understand the different roles and loyalties of treating physicians and researchers and that these roles are created by the very act of randomization. In every case of randomization the difference is stark: the treatment the person will receive is not chosen because it is considered the best treatment for the individual patient by the physician who has a fiduciary duty to the patient, but rather is chosen by a protocol designed by people who have no relationship of any kind with the subject.

This is further complicated by the fact that it is rare that there is not some medical consensus that one form of treatment is superior to the other. A good example of this is found in the SUPPORT study where the research protocol indicates that the more "conventional treatment" was to provide very premature infants with higher saturations of oxygenation than the lower saturation provided by some physicians.[5] It is essential that subjects be informed that they are at risk of not receiving what is considered "the more conventional treatment" or the treatment that many doctors consider to be the superior treatment. While it may turn out that the treatment considered superior is in fact not superior to the alternative treatments, this will only be known in retrospect, and subjects need to be aware of what the best judgment of their treating physicians is at the time of enrollment.

The risk presented by randomization for the determination of which medical treatment a person will receive is always more than "minimal risk." According to current federal regulations minimal risk means "the probability and magnitude of harm or discomfort anticipated in the

[5] Protocol for the NICHD Neonatal Research Network, The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants, p. 9, March 28, 2013.

research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Once again we note that the terms "risk" and "harm" are not confined to physical risk and harm. The harm from randomization, as discussed above, is that patients will not receive the care their physicians consider to be in their best interests. Receiving medical care that is randomly chosen is not something one encounters in "everyday life." We think that most patients would be shocked to discover, after the fact, that the treatment they received was determined by a stranger who created a protocol rather than by their treating physician's best judgment. This risk is clearly greater than minimal risk in terms of respect for persons.

IRBs should *never* be allowed to waive informed consent for research involving randomization of individual subjects into "standard of care" interventions. Failure to inform research subjects that they actually are research subjects is the epitome of disrespect for persons. The failure to discuss randomization with potential research subjects would result in using people for research purposes without their knowledge. If there is anything that research ethics requires, and that IRBs must enforce, it is the principle that every person who is a research subject must be aware that they have been recruited into that role. People should not be treated like laboratory animals, as a means to an end, and that is how they are treated in the absence of their knowledge and consent.

How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions? What if the risk significantly varies within the standard of care?

If there is no uncertainty about the risks and benefits of various forms of "standard of care," then there is no justification for conducting the research at all. It is the very existence of uncertainty about both the risks and benefits of different types of care that both justifies the

conduct of the research and requires that subjects be fully informed of these uncertainties. The more significant the risks and benefits of two interventions differ, the more essential it is that potential subjects be made aware of these differences and of their option to receive what their physician considers the best care. As an obvious example, if a study involves randomizing people to determine which of two accepted forms of treatment is most likely to prevent death, it would be clearly unethical for research subjects not to be informed that death is the outcome measure for the study.

Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases the risk of harm, or is it necessary that there be published studies identifying the risk?

As we stated in our introductory comments, there is nothing special or even "scientific" about the adoption of "standards of care." When physicians adopt a standard of care it is based on, at least in part, their assessments of risk and benefit. The fact that numerous methods for providing care have not come about as a result of rigorous scientific study of risks and benefits does not mean that there is not substantial experience in the community of physicians of the risks (whether "documented" or not) inherent in a standard treatment.

One of the reasons physicians adopt particular standards of care is that the combination of biological plausibility and experience have provided some information of the risks and benefits of a particular treatment approach. As an example, in the SUPPORT trial it was clear that at least some physicians were concerned that lower oxygenation levels in very premature infants increased the risk of mortality, which is why the "more conventional" treatment was the use of high oxygenation. On the other hand, there were physicians who were concerned that high oxygenation might lead to increased blindness and therefore they might choose a lower level of

oxygenation. These different approaches and concerns about risks and benefits were the very reason there were differing standards of care in different institutions. Whether or not these harms were in the peer-reviewed literature or otherwise documented, parents should be made aware of the reasons different physicians use different treatment approaches, and the risks each choice presents.

Conclusion

The practice of medicine should be evidence-based and comparative treatment studies are an important way to obtain some of this evidence. We do not suggest that comparative effectiveness studies should be stopped or that they are inherently unethical. But it is essential that the utility of such research not blind investigators, IRBs or federal regulators to their obligation to ensure that the rights and welfare of research subjects are protected. Such protection is not limited to reducing or eliminating the chances of physical harm, but must also eliminate the risk to human dignity that is threatened whenever humans are used merely as a means to an end without their knowledge and voluntary informed consent.

There is nothing meaningful that distinguishes comparative effectiveness research from any other form of research with humans that would justify waiving basic informed consent requirements – it is simply one type of research methodology. As with all forms of human research methodologies the risks to the rights and welfare of human subjects are dependent on the specific facts of the case. For example, research using a placebo control arm for people suffering from a curable infection would clearly be unethical. But this does not make all placebo-controlled research unethical. The same is true of comparative effectiveness research. Each study must be reviewed based on its specific goals, outcomes, risks and benefits. This review

must be conducted in an atmosphere in which the rights and welfare of research subjects take primacy over an investigators needs, or even over the benefit the research may provide to others.

Respectfully submitted,

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Note: The opinions expressed in this document are those of the authors, all of whom work at Boston University, but do not speak for Boston University.

PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 01, 2013
Status: Posted
Posted: August 07, 2013
Tracking No. 1jx-86sd-34pg
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0006
Comment on FR Doc # 2013-15160

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General Comment

For Public Responsibility in Medicine and Research's (PRIM&R's) comments, please see attached file.

Respectfully submitted on behalf of the PRIM&R Board of Directors,

Elisa A.Hurley, PhD
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Attachments

PRIMR_OHRP Response_Research on Standard of Care

PRIM&R

PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

August 1, 2013 Submitted electronically at www.regulations.gov

The Hon. Howard Koh, MD, MPH
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RE: **Docket HHS-OPHS-2013-0004**, Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions (78 FR 38343).

Dear Dr. Koh,

Public Responsibility in Medicine and Research (PRIM&R), a nonprofit educational and professional development organization, appreciates the opportunity to submit comments on matters related to the protection of human subjects of research when studying standard of care interventions, as requested in the June 26, 2013 *Federal Register* notice.

For 39 years, PRIM&R has been dedicated to advancing the highest ethical standards in the conduct of research. We accomplish this goal by serving the full array of individuals and organizations involved in biomedical and social science/behavioral research, particularly the members and staff of human research protection programs (HRPPs) and institutional review boards (IRBs). Through conferences and other educational activities, PRIM&R provides balanced, thorough, and accurate information on a range of ethical and regulatory issues affecting research. As a result, we have developed a good sense of what is important to the frontline defenders of ethical research practices.

I. Introduction

Before making specific recommendations for the Office for Human Research Protections (OHRP) guidance to IRBs, we wish to make a few preliminary points.

First, PRIM&R believes that 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 may be. Nothing about the work that is the topic of the present notice, "research studying standard of care interventions," justifies departing from this basic precept. A primary mechanism by which such protection is operationalized is informed consent. When it is working as it should, the informed consent process provides in a clear, well organized, and accessible way the information a potential subject needs to make a considered decision about whether or not to enroll in a research study. While the Common Rule lays out required elements of informed consent, we believe it is essential that all those involved in human subjects research understand that adherence to a regulatory formula is not the same as achieving voluntary and informed agreement, which involves a process, appropriate to the level of risk and burdens implicated in the research, that is

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thorough, transparent, and sensitive to the situation of each potential subject, particularly those who are also patients.

Second, investigators who undertake research with patients must be especially vigilant about potential gaps in or failures of understanding, and must thus be sensitive to the circumstances that may exacerbate such gaps or failures. Written consent forms alone are rarely if ever adequate for informed consent. Additional, creative efforts to assess and ensure adequate comprehension of the options around enrolling in research may be called for, and obtaining consent from patients or other vulnerable subjects (or their surrogates) commonly requires devoting substantial time and energy to an ongoing consent conversation. Investigators and their research teams should be expected to make this effort.

II. Guidance for IRBs Evaluating Studies involving Standard-of-Care Comparisons

Given these precepts, we propose a framework to guide IRBs when they are asked to review research involving random assignment of patient-subjects to interventions all of which fall within the "standard of care" provided to patients outside a trial. Our terminology follows that of the *Federal Register* announcement. First, we use the term "intervention," which encompasses diagnostic and preventive as well as therapeutic measures, since all may be the subject of comparative study. One difficulty with the term "intervention," however, is that in some situations, it might suggest that what is being compared is an individual item (*e.g.*, one type of syringe versus another). By medical interventions we have in mind not such individual items but clinical regimens (sets of procedures designed for particular clinical ends). Single items may need to be evaluated for their efficacy and safety, but comparative effectiveness trials usually involve multipart regimens. Furthermore, we assume that what is being studied involves something about which patients usually choose among alternatives, that is, the sorts of changes in routine care that are first discussed with patients by the physician because they would be material to patients.[1]

The other phrase in the *Federal Register* announcement, "standard of care," could also be criticized in the present context. Since a common use of "standard" is a rule set by an authority (*i.e.*, a bureau of standards), it seems hard to explain why one would intentionally deprive patients of an intervention that embodies the "standard."[2] A good deal of evidence—particularly evidence of efficacy derived from clinical trials conducted with a carefully select group of subjects—exists for

[1] Other sorts of matters—how the facility maintains hygienic conditions, how nurses distribute medication, which scalpel is used in an operation, and the like—are covered by the general consent (implicit as well as explicit) that patients give upon entering a healthcare facility. Of course, even within this ambit, physicians, nurses, and healthcare administrators are responsible for the consequences of the professional choices they make, and if a change they have made unreasonably increased the risk of injury they can be found liable for any resulting harm, though not based on the failure to have received informed consent for the change.

[2] A similar criticism was raised when "standard of care" was used to indicate the care that had to be used in the control arm of a clinical trial of a drug for which treatments already exists. This alternative to using a placebo control was often taken to mean the best treatment for the condition in use anywhere, although the National Bioethics Advisory Commission argued that it would be acceptable to give any "established effective" intervention to control arm subjects in a setting where little or no treatment for a condition is generally available. National Bioethics Advisory Commission, Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (2001), pp. 22 ff. "Established effective" would, however, seem inapt in the present context, when interventions are subjected to comparative study precisely because their relative effectiveness has not been established.

many of the interventions routinely used in medical treatment. What is missing, however, is adequate information about the effectiveness of many interventions as they are generally used, often for indications and in populations for which clinical trials have not been conducted, much less trials that would allow interventions to be compared reliably to one another. In these circumstances, a range of interventions are all within the standard of care. Thus, despite the potential ambiguity with the term, we follow the Department's lead and use "standard of care" to refer to medical interventions that are routinely used by a recognized group of qualified practitioners in treating the condition being studied in the relevant population. Trials of this sort are conducted when uncertainty exists about which of two or more widely used interventions better achieves a particular set of outcomes.

Below are six questions we recommend that IRBs ask concerning protocols and informed consent processes in such trials. We provide further explanation and justification for each question.

1. **Have the investigators established that the medical interventions being compared are within the accepted "standard of care" for the population being studied and that doubt exists concerning their relative effectiveness?**

   In reviewing a study comparing standard-of-care interventions, the IRB should ensure that the investigators have adequately supported two threshold points: (1) that the interventions being studied are indeed within the accepted standard for the proposed study population, and (2) that adequate evidence is lacking as to which intervention is most successful in producing particular outcomes, including considerations of burdens and potential harms and benefits. Typically, the first will involve the investigator providing the IRB with professional practice guidelines, data on actual physician practices, or other evidence from peer reviewed journals and medical textbooks relevant to establishing the accepted use of the interventions in the population in question (which should include information on the safety and effectiveness of the interventions).

   The second point can be addressed by published commentary on the existence of disagreement regarding the superiority or inferiority of the interventions or any other legitimate source of information that justifies the need for the comparative research. An IRB may need to consult experts in the relevant field of practice for advice on the completeness and persuasiveness of these materials in order to answer these two threshold questions, but in some cases, the answers may be inferred from the very fact that the protocol involves a multi-site study funded by a national medical research body which has subjected the protocol to extensive peer review before being willing to fund it. In examining the two threshold issues, the IRB is not setting itself up as a scientific review body, because deciding whether those with expertise are satisfied that adequate justification exists to provide these particular standard-of-care interventions in a research rather than clinical context is ultimately an ethical judgment.

2. **How will potential subjects be informed about the nature and potential harms, burdens, and benefits of the medical interventions being compared?**

   In providing interventions in the context of ordinary care, physicians are generally expected to engage patients in a discussion about the nature of the intervention and any other routinely used alternatives and their relative burdens and potential harms and benefits. 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, potential benefits, harms, and burdens of the interventions being compared in the trial. This would usually be a member of the research team providing the interventions, but sometimes the discussion of the alternatives in a therapeutic context may initially be carried out by the patient's treating physician before the patient is referred to the research team to discuss entering a trial that will compare two or more standard-of-care interventions for the patient's disease or condition. From an informed consent vantage point, the central concern is that all the relevant factors about each intervention (and especially its potential harms or burdens) be conveyed in as clear and comprehensible way as possible to the patients (or surrogates) who are being solicited to become subjects in a study of those interventions.

Investigators should explain how this process will be carried out, and IRBs should consider such descriptions carefully but also creatively. Guidance rather than regulations is needed because this process of disclosure and discussion can vary from setting to setting and from intervention to intervention, based on the disease or condition being treated, diagnosed or prevented, the relative complexity or familiarity of the interventions, the nature of their potential harms and benefits, the clinical setting, and the prior relationship, if any, of the participants (patients, physicians, investigators, and so forth). The process may involve explanatory materials, written consent forms, oral presentations (with the points to be covered specified, but the exact sequence and format shaped by each particular physician-patient encounter), or other forms of communication (such as interactive media).

Before they become research subjects--indeed, preferably before they are invited to become research subjects—patients should have a clear picture of the risks that inhere in the interventions when they are used in routine medical care. This understanding is especially important when these risks differ in type—that is, when the potential harms of the alternative interventions involve trade-offs among different categories or degrees of harm. In such a situation, a patient may strongly prefer one set of burdens and potential harms and benefits over the other, and thus would probably not want to be in a research project in which he or she has an equal likelihood of being assigned to receive the intervention that is more likely to produce the disfavored risks.

3. **How will the potential subjects be informed that they are being asked to be part of a study comparing two medical interventions and that if they do not wish to participate in (or, later, to continue in) this study, they will instead receive standard care?**

The essential predicate for a patient being enrolled in a study comparing two or more standard interventions is that the patient knows what will be entailed in entering the study: namely, that the intervention he or she receives will be determined under the protocol (typically by random assignment), that the person providing it will be an investigator rather than simply a treating physician, and that the research may impose particular burdens and potential harms beyond those involved in receiving the interventions solely as ordinary care (a point addressed in question #5 below). The IRB should ensure that there is a plan or process in place for informing potential subjects that they are being asked to participate in research. Furthermore, in order for subjects to make an informed decision about participating, they 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 facing potential subjects is whether they wish to have the intervention that their physician recommends based upon the physician's best (albeit less than fully supported) clinical

judgment or whether they—out of a desire to help develop medical knowledge or frustration with the lack of adequate comparative information to guide them and their physician in making choices about their own care—are willing to have the intervention chosen by a process governed by the rules laid out in the study protocol.

For the IRB, the central goal should be to ensure that the investigator has set forth how potential subjects will come to understand that they have a *choice* as regards the specific interventions being studied between remaining in a therapeutic, doctor-patient relationship, or entering an investigator-subject relationship, in which case their physician will not routinely be making personalized clinical decisions about the use of the interventions under study. The usual reassurance given to potential subjects—that the decision to decline participation in a study will not adversely affect their treatment—is particularly pertinent here because patients who decide not to enroll in a trial comparing two standard-of-care interventions should still be able to get either intervention outside the trial since they are routinely used in clinical practice, in contrast to the situation in trials of new drugs and devices that are not yet in general use. As always, patients who choose to enroll must also be told that they can choose to terminate their participation in the study at any time, in which case they will return to having their care governed by the best judgment of their physician(s).

4. **How will the potential subjects be informed of any available alternatives (and their potential harms and benefits) to the interventions being offered in the study?**

In order for consent to participate in research to qualify as informed, potential research subjects must be adequately apprised of the alternatives to participating in the study. When the alternative to participating in research is receiving one or more treatment that is also the object of the study, there is greater potential for confusion about the differences between participating and not participating in the research. These differences must be fully explained to the potential subject, a responsibility that falls to the investigator. It is incumbent upon the IRB, through its oversight function, to ensure that both the informed consent process and the form include a very clear statement that the alternative to enrolling in the study—where the specific intervention a subject receives will be decided randomly—is to leave the choice in the hands of a physician using his or her best clinical judgment. At the same time, it is important for prospective subjects to understand that, given the lack of definitive evidence about which intervention is best, a physician—however good his or her intentions—cannot know whether the intervention he or she recommends will actually serve the patients' interests better than the alternative. These statements should be accompanied by an explanation of what is known about the potential benefits and harms (per #2 above) of each possible intervention.

5. **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 potential harms beyond those that inhere in each intervention when provided as part of standard care requires complicated and nuanced assessment. An IRB must determine whether the investigators (1) have thoroughly examined and identified the added burdens and potential harms to subjects that are added by participation in the study, over and above the risks of receiving either of the standard-of-care interventions being compared, and (2) have developed an adequate description of those added risks for the informed consent process. The specific potential harms added by research participation will necessarily be case-

dependent. However, we urge OHRP to provide guidance to IRBs about how to identify and then evaluate those additional burdens and risks, as illustrated by the following examples:

- Some burdens and potential harms may arise because subjects in the study will undergo additional testing and monitoring (ranging from extra blood-draws and spinal taps to diagnostic imaging), which may create new burdens and potential harms to which patients receiving the intervention as ordinary care would not be exposed.
- Some potential harms may arise because in the course of ordinary care the level or type of a specific intervention would be modified in light of an individual's response to the intervention or what the physician knows about the patient's preferences, whereas in research the study interventions will be given according to the protocol which may or may not provide much flexibility for investigators to respond to the evolving situation of individual subjects. In general, study protocols tend to be more rigid than management by one's personal physician, so it will be important for the IRB to be satisfied with the point specified by the investigator when a subject's response will be judged to be so far off the expected range that the subject will be withdrawn from the study and treated simply as a patient. As part of the obligation to minimize harm to subjects, physician-investigators always retain the authority to exercise their Hippocratic duties to subjects as patients and change the interventions being used when necessary to protect the patient's well-being.
- As a result of procedures that mask certain data sources, a physician-investigator may not receive information he or she would have received when providing ordinary treatment, giving rise to additional risk.
- All studies with random assignment also pose the risk that, should the intervention that a patient-subject would have received outside the research (*i.e.*, the intervention usually recommended by the patient's physician) be proven by the research to be the superior one, the subject has an even chance of not having received that intervention. Of course, the obverse is also true: should the intervention the patient would have received outside of research turn out to be the inferior one, the study will have offered the patient-subject an even chance of getting the superior intervention. The question for a potential subject is thus whether he or she would find it easier to accept a bad outcome that results from a medical intervention that was chosen by the physician and patient than if it were produced by having been randomly assigned to the group that received that intervention.

6. How will the potential subjects be informed of any such additional risks?

Similar to our response to question 2, subjects in studies comparing two or more standard interventions should be informed of risks using methods traditionally employed to obtain informed consent from all potential research subjects. The IRB should ensure that, if and when additional risks of research participation are identified, the informed consent process and form include (1) a clear statement that participating in research involves potential harms over and above those receiving one of the interventions outside of the research, and (2) a clear and complete description of those additional risks.

III. Research to Achieve a "Learning Health System"

The activity that provoked OHRP's present enquiry—namely, comparative studies of standard-of-care interventions—is part of a broader, and growing, interest among clinicians, health systems researchers, and healthcare funders (including the Federal government) to improve the efficiency and effectiveness of health care by remedying the alarming lack of evidence for much of what happens in medical practice. A variety of activities designed to address this gap and compare the effectiveness of health interventions have recently emerged across the healthcare landscape. The type of research on which DHHS is seeking guidance for IRBs is just one of many such activities. Others include pragmatic clinical trials engaging large health care systems and learning healthcare systems that aim simultaneously to provide care, study outcomes, and improve practice. As the Patient-Centered Outcomes Research Institute (PCORI) gains momentum, we will see a move toward a healthcare system that mandates large-scale projects, including retrospective examinations of health data and interventions designed to determine the optimal standard of care.

As these activities become more widespread, it will be important to establish appropriate oversight systems. Only some of these activities qualify as research under the current regulatory definition, but all face a number of regulatory and ethical challenges including what, if any, type of ethical review is required and what to do when it is not feasible to obtain individual informed consent. It is unclear how to re-conceive models for appropriate oversight for circumstances such as these in which risk, if any, may be minimal but benefit for society is potentially great.

PRIM&R is already involved in several projects identifying and examining the ethical issues that arise for activities designed to learn from the results of providing routine health care and initiating clinical innovations, and we hope to provide guidance to the HRPP/IRB community as our work progresses. We encourage OHRP to use its considerable authority to anticipate the need for ethical guidelines around these emerging learning activities.

IV. Conclusion

Practicing medicine on a strong evidence-base is essential if scarce resources are to be used in the most patient-centered manner possible. Seeking to fill gaps in our knowledge about the relative merits of different, accepted interventions for a particular condition is an important tool for adding to that evidence-base. However, research to improve our understanding of the correct standard of care (often called comparative effectiveness research) is not unique from the perspective of research protections. Those seeking to enroll patients in a study to compare standard-of-care interventions must explicitly tell them that they are being asked to participate in research and what this means for them. Unless a study meets the criteria for an informed consent waiver or exemption, prospective subjects must be informed in a comprehensive and transparent way about the nature, risks, and benefits of the interventions being studied and about any added potential harms or burdens presented by the research, as well as about alternatives to research participation. It may be more complicated for IRBs and investigators to apply the Common Rule and general ethical guidelines about risk and informed consent when research involves standard-of-care interventions, given the added complexities of identifying the relevant standard, of clearly separating the potential harms of the existing interventions from those added by enrolling in the study, and of adequately explaining to subjects the differences between receiving an intervention as a physician's *patient* and receiving possibly that same intervention as the *subject* of a clinical trial.

We hope that our specific suggestions for how IRBs should be encouraged to think about trials comparing standard-of-care interventions so as to ensure that they meet the high ethical

expectations of the Common Rule, as well as our framing comments in sections I and III, are useful to the Department and to OHRP as you develop guidance or propose modifications in the regulations. As always, PRIM&R stands ready to assist the Department and OHRP with the development of a framework for the ethical oversight of research with human beings that is appropriate to the particular types of research being proposed and carried out. We look forward to an opportunity to discuss this goal with you and to collaborate with the Department and with OHRP on achieving it, which is a matter of central importance to our members.

Respectfully Submitted,

Alexander M. Capron
Chair, PRIM&R Board of Directors

cc: Board of Directors, Public Policy Committee

PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 07, 2013
Status: Posted
Posted: August 08, 2013
Tracking No. 1jx-86wl-jau6
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0019
Comment on FR Doc # 2013-15160

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General Comment

Comments on behalf of the leadership of the Cinical Research Ethics Key Function Committee and the Child Health Oversight Committee of the CTSA Consortium.

Attachments

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for Pediatric Bioethics

August 7, 2013

Comments for HHS Public Meeting
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HHS-OPHS-2013-0004

These comments are submitted on behalf of the leadership of the Clinical Research Ethics Key Function Committee and the Child Health Oversight Committee (CC-CHOC) of the Clinical and Translational Science Award (CTSA) Consortium, supported by NIH. We are individuals working at academic medical centers who are committed to advancing ethically sound and socially responsible research to improve health. These comments are not the official views of the NIH, the CTSA Consortium or our institutions, nor do they represent the views of all the members of our groups. These are critical issues that are complex and have only recently been the subject of scholarship and analysis. We anticipate that further research and analysis will be necessary and welcome this hearing as an important first step in that direction.

We initially will acknowledge two perspectives, offer two overarching comments, and present a vignette to help frame our responses to the questions. Our substantive comments will focus on the first three questions posed by HHS for today's hearing.

Our first perspective is from the vantage point of the CTSA Clinical Research Ethics Key Function Committee, which includes more than 150 members from 61 academic institutions throughout the US with the mission to expand the use of best practices in clinical research ethics. We accomplish much of our activity through working groups, two of which highlight useful approaches to the questions posed by OHRP. 1) Our **Ethics and Community Engagement** working group is committed

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to community involvement in all aspects of research. Input from the public, including potential research subjects, will be critical to interpreting federal policy for the protection of human subjects in ways that are acceptable to all and that further the public interest. Community engagement can provide important insights into specific research projects on standard of care when traditional approaches to informed consent are challenging. 2) Our **Consultation** working group is a network of individuals who provide research ethics consultations to researchers and IRBs at CTSA institutions. We have found that sustained deliberation over time with input from all relevant stakeholders can be useful when navigating novel moral terrain. We would encourage OHRP to consider how to convene content experts when new issues arise.

Our second vantage point is from the CC-CHOC, composed of 237 members from the 61 institutions who are committed to improving child health using the scientific method. The traditional exclusion of children from clinical research has resulted in an even larger proportion of clinical practice provided without an evidence base than for adults. The great majority of drugs and devices used to treat infants and children have not been studied adequately for safety and efficacy in those populations, so the deliberations here are particularly germane and standard of care research is critically important.

Our first overarching comment is that there is growing appreciation that the current approach to informed consent has serious flaws. Clinical studies are becoming increasingly complex. To understand them, one must process a great deal of background information, appreciate statistical probabilities, and know the difference between the use of non-validated therapies and clinical research. As a result, informed consent documents are lengthy and difficult to understand. Numerous studies show that people can participate in the informed consent process and still retain misunderstandings about the most basic facts about the research for which they have given consent. Further, while the informed consent process is meant to inform, engage, and empower potential research subjects, consent forms serve other goals (i.e., administrative and legal) as well. As we think about ways to improve the process of giving information and seeking consent, it is important that we think about the underlying rationale behind the

consent process and about the range of approaches to engaging participants respectfully and meaningfully. We are skeptical that patient engagement can be accomplished by appending additional information to consent forms that are already too long and too complex. Alternative means of engagement using web, video, graphic communications, and social media may be more useful than 10- to 20-page consent forms, especially with participants or surrogates who face highly stressful circumstances.

Our second overarching comment is that the concepts used to guide our standard approach to informed consent—i.e., risks related to research, foreseeable risks, minimal risk, and waiver of informed consent—are intrinsically connected to the regulatory framework. As illustrated by the advanced notice of proposed rulemaking in 2011, the US regulatory framework is being reconsidered. Although our comment uses this regulatory language, we emphasize that the issues related to "standard of care research" or "comparative effectiveness research" transcend this framework.

Our vignette (to which our remaining comments refer) is an example of a randomized clinical trial related to standard of care.

In the early 1980s, several countries and Colorado and implemented newborn screening (NBS) for cystic fibrosis (CF) as a "standard of care." Researchers in Wisconsin decided to study this new intervention with a randomized clinical trial. From 1985 to 1994, 650,000 newborns were screened for CF in Wisconsin. Half of the results were returned within six weeks, while the results for the other half were disclosed at four years of age. This study underwent NIH and IRB review as well as extensive community engagement and ethics consultation. It was conducted with a waiver of informed consent for screening, but a more detailed informed consent process was used for diagnostic testing and for treatment of identified CF patients with standardized treatment protocols. The study yielded important information and could not have been done logistically without a waiver of consent. In 2004, a CDC Workshop concluded that newborn screening for CF was justified. Today, all states screen newborns for CF.

There were unforeseen harms during the study. Some children in the group whose positive screening results were revealed at six weeks had worse pulmonary outcomes than those diagnosed at age four. The children identified with CF at six weeks were sent to a specialty clinic for treatment, where some were unintentionally exposed to *Pseudomonas* bacteria from other children. Children diagnosed at age four avoided that early exposure. Measuring *Pseudomonas* acquisition was one of many surveillance aspects of the protocol, but *Pseudomonas* acquisition was not an identified risk and participants were not told that infection was a risk of being in the study. This was not expected because of limited knowledge of appropriate infection control procedures.

Some lessons from the CF newborn screening study are:

- There can be unforeseen risks in standard of care research.
- Some of these risks are the risks associated with standard treatment. These risks are recognized because of the research. The harm in the CF research was also a harm of standard therapy, and the study led to reduction of risk and improvements in care for all the children of Wisconsin, as well as around the country.
- Many parents of newborns did not understand the study. Efforts at community engagement and public education are inadequate and need to be improved.
- Sometimes waivers of consent for randomization are appropriate, ethically defensible, and necessary.

1. How should IRBs assess the risks of standard of care interventions provided to subjects in the research context? The risks of standard practice can be quite significant, particularly for seriously ill newborns and children. Efforts to provide and improve care can be helpful or harmful whether or not these efforts are within the context of research. It is important that patients and parents are informed of specific risks and benefits of proposed treatments. When reviewing proposed standard of care research, IRBs should be aware of these risks and ensure that the balance between clinical benefits and harms is

favorable. The risks and benefits of clinical treatments are NOT risks of research. The risks of research are only those risks that are associated with the portions of the research protocol that are not part of conventional clinical practice. IRBs also should consider their role in conjunction with institutional bodies responsible for clinical quality improvement planning and implementation. It is important to help patients understand the risks and benefits of standard treatments, but we do not think that this will be well accomplished by including substantially more information in consent forms. Nor, do we think that failure to include risks associated with standard interventions in the consent forms suggests that informed consent was not adequately obtained. In some cases, the same outcome can be inversely described as a benefit or a risk, and it is not clear how best to communicate this to participants.

It is important to remember that in a clinical context, there often are numerous conversations about the risks and benefits of conditions, treatments, and alternatives. During the treatment phase of the CF newborn screening trial, the potential risks of having a diagnosis of CF included hospitalizations, ICU admissions, and even death. These were not considered to be risks "of" the research even though these risks were present "in" the research; the purpose of the research was to learn if newborn screening would improve the health of children with CF and thereby justify a significant public health effort.

2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects? The critical aspect of this question focuses on what should be disclosed to subjects. The expected risks of research should be disclosed to subjects (or their parents/legal guardians) to help them make decisions about research participation. Expected risks are those that can be reasonably foreseen and that are related to research. As stated above, some risks are not expected and other risks are not related to research. In the ICU, where death is a potential outcome, it will always be necessary to measure death rates, but it does not necessarily follow that death is a foreseen outcome of the research. In the Wisconsin newborn screening study, death rates

were measured during the screening and treatment phases, but death was not a foreseen risk of the research nor disclosed as a risk of the research.

In standard of care research, where the goal is to see whether one approach will be better than a different approach, it remains unclear how best to frame this for patients. We could say that our objective is to see whether one approach is *better* or if one is *worse.* These outcomes are inverses. We need to learn more about how best to convey this insight to participants and, without further empirical research on the issue, we would be reluctant to conclude that simply listing the inverse of benefits as risks will promote such understanding.

3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? The concept of randomization is complex and much social science research has suggested that participants often are confused about what it means and why it is done—in spite of substantial efforts to explain it. We believe that further efforts to learn how best to explain and communicate the meaning and purpose of randomization are important. But how to explain randomization is distinct from whether it should be considered a risk. Explicit randomization to two different approaches offers no more risk than relying on random, unscientific reasons for selecting different treatment approaches. Using our CF screening example, in 1990 all babies in Wisconsin were randomized to one of two schedules for reporting screening results, while in Colorado all babies were screened, in Maryland no babies were screened, and in Connecticut babies in a few hospitals were screened. While the risks and benefits of screening were unknown at the time, we do not believe that randomization itself introduced any additional or unique risk.

Under the current regulatory framework, IRBs are able to "waive informed consent" for randomization of standard of care research in certain circumstances. However, there are ethical obligations to consider when pondering how best to communicate and engage patients about this process. Although consent was waived in the CF newborn screening trial, all parents were notified about the study and

parents could "opt out" by requesting their results. (As the study was designed, parents could not opt out of testing, they could only opt out of being blinded to the results.) One crucial lesson of the CF trial was that most parents remained unaware of the study. Clearly, better efforts at public engagement are essential in every study but particularly in studies done with waiver of consent. Patients at hospitals where such studies are being conducted should know that standard of care research with randomization is occurring, that the research design has been carefully reviewed before being implemented, that they are involved in an important effort to improve care (which may not benefit their child, but may provide benefits in the future), and that the research involves treatments that are in routine clinical use. We think that such awareness has the potential to improve patients' confidence in our health care systems and promote public trust in biomedical research.. Requiring explicit patient consent forms for each randomization activity creates an administrative burden on patients and researchers that is not likely to promote such confidence. More social science research is necessary to determine how best to engage patients.

In summary:

1. The risks of standard treatments are NOT risks of research. Research comparing two non-validated treatments is the best way to identify those risks.
2. Studies sometimes "uncover" harms that are associated with non-validated treatments. This is one reason why such studies are important.
3. Patients/parents do not understand research well and the current approaches to informed consent are not effective in improving understanding.
4. We need new approaches to the informed consent process that are more flexible, more focused on helping prospective study subjects truly understand the most crucial elements of research, and that are developed in conjunction with the relevant patient communities.
5. Sometimes consent can be waived—but this, too, requires active and innovative community engagement and alternative ways to reach those patients.

We applaud OHRP and HHS for organizing this meeting. These issues are complex and we anticipate that we will learn from others' comments and that our views likely will change over time. We do not foresee that this meeting will be a sufficient basis for OHRP to issue guidance. We think that iterative deliberation among researchers, scholars, regulators, patient advocacy groups, patients, and the public will be necessary. In addition, more empirical social science research must be conducted regarding public views and concerns about research and experiments with novel approaches to informed consent and the engagement of patients. Our primary goal remains to improve the health of the nation and we are committed to working closely with you and to participating in any future discussions on these crucial issues.

Sincerely,

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PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 07, 2013
Status: Posted
Posted: August 08, 2013
Tracking No. 1jx-86wj-sitr
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0017
Comment on FR Doc # 2013-15160

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General Comment

See attached file(s)

Attachments

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August 7, 2013

Comments for HHS Public Meeting

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HHS-OPHS-2013-0004

These short comments are submitted on behalf of myself, David Magnus, PhD. While the content reflects and benefited from relevant discussion with a number of others, particularly members of the compliance community at Stanford University and Drs. Ben Wilfond, John Lantos, Chris Feudtner, Art Caplan and many others.

1. How should IRBs assess the risks of standard of care interventions provided to subjects in the research context?

I will focus my comments on prospective, randomized research among standard of care interventions. The first issue that needs clarification is the meaning of "risk." There is a good deal of philosophical and technical discussion about how to interpret risk. For these purposes and reflecting the majority view of risk, risk is about assignment of an expectation value for an event. The expectation value is the product of probability of a harm occurring and its severity or magnitude. When discussing the risks of research it is actually difference in risk (changes in probability or severity of harm) as a result of engaging in research that is at stake.

There has been some confusion in discussion of risk in research with insufficient attention paid to the difference between risks of the various treatment options that exist for a given condition (that is being studied); risks of the arms of a study that falls within the standard of care (which may or may not be the same as the latter as SUPPORT demonstrates); and risks of enrolling in a research study as a participant versus receiving standard of care. I argue that it is the latter that is relevant for the purposes of IRB review. In assessing the degree of risk, the right question to ask is whether, based upon knowledge reasonably available to IRB's and investigators at the time, there is a reason to believe that the expectation value of any defined negative outcome (defined as the produce of probability of a negative event and the

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severity of the harm) is greater to those who agree to participate in research versus those who do not. If there is no expected difference then there is no difference in risk. For example, if A and B are two drugs to treat hyperthyroidism, and there was no evidence about which was better (and both were in common use) there is no increase in risk to being randomized between A and B versus exogenous factors determining which drug a patient receives.

There are several reasons why this is the right way to look at this question. First, it avoids making research sound riskier than it really is (i.e. than clinical care that the patient was going to receive anyway). Informed consent forms (and the more important informed consent process) are there to help ensure that patient autonomy is respected and to protect research participants from harm. Falsely, making research sound riskier than the risks the patient participants will be exposed to anyway fails to protect participants, but potentially could slow the progress of incredibly important research.

Second, recognizing that risk is about the difference between the expectation value of negative outcomes for participants versus non-participants focuses on the relevant difference between the relevant populations (those who are to be enrolled in research versus those who are not). The other alternatives parse the populations for risk assessment in ways that are not relevant to whether someone is enrolled in research or not (and apply equally to those receiving standard of care).

Third, conflation of the risks (and benefits) of standard care that the patient was going to receive anyway with the risks of participating in research can be exploited. For example, a number of years ago, researchers were doing gene transfer research on brain tumors, using vectors to deliver part of the human herpes simplex virus that expresses thymidine kinase (HS-tk)to the cancer cells. Participants would take ganciclovir (GCV) in an attempt to kill off the tumors. In order to deliver the vector to the tumor site, the research required that patients first undergo a de-bulking procedure that was standard of care for patients with these forms of incurable cancer. That is, the patients would have received the de-bulking procedure whether they were enrolled in research or not. Nonetheless, the procedure was included in the protocol. By the time this research was being conducted, there was fairly good evidence that the HS-tk GCV model was not going to work in humans. But researchers at the time claimed benefit to being enrolled by virtue of the de-bulking procedure that they would have received anyway. This is wrong. The risks and benefits of research should be seen as those related to what makes the difference—being in research and they ways that varies from what they would otherwise have received.

2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research

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context, are reasonably foreseeable and therefore required to be disclosed to subjects?

From the fact that a particular study is minimal risk, there are implications for consent, but there is clear room for greater guidance here. Again there is a distinction between disclosing the risks of participating in the research; the risks (and benefits) of standard treatments (that patients in research within the standard of care will be receiving); and risks of the different arms of the randomized protocol. When is it appropriate for IRB's to consider waiving informed consent for minimal risk research within the standard of care? What should go into the consent forms?

I suggest that IRB's should be given guidance to direct their attention to the challenging issue of commensurating the severity or magnitude of harm associated with different expectation values. IRB's are constantly required to make judgments about equipoise and whether risks are reasonable in relation to anticipated benefits. These activities require commensurating differences in severity or magnitude of harms and benefits that may be valued very differently by different individuals. For example, if there is a very small difference in risk of death but a very great difference in quality of life, IRB's may have to decide whether the magnitude of harm is equivalent to allow a trial to take place. Researchers and IRB's considering equipoise must often weigh outcomes that are more challenging to commensurate to arrive at a communal judgment of the relative risk of two options. This is one of the reasons for local IRB review, since local values may lead to different ways of making these valuations. For research within the standard of care, sometimes the task of commensurating risks is fairly straightforward. If the only significant difference between two treatment options is about which is more effective (and that is not known) then there is very little basis for any view that an individual research participant (or patient) might have for why they would prefer one treatment option to another. In these cases, if there is no other way for valuable research to take place, it is appropriate for IRB's to consider waiving documentation of informed consent and also for considering expanding the scope of consent practices (disclosure versus consent; broad consent by patients to be randomized within standard of care at point of care).

But, if there are significant differences in the way individuals are likely to value the severity of harms, which should inform what goes into informed consent. To be clear, this does not imply that such research is necessarily more than minimal risk. If the product of the probability of harms and their magnitudes (as reasonably judged by an IRB) are equivalent, they may have the same degree of risk -- but if individuals are likely to value the magnitudes differently, then respect for the autonomy of participants requires a fuller consent process and it is appropriate to require documentation of informed consent and to insist that these relevant differences in outcomes be included. They are compatible with stating clearly that the research is

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minimal risk in the consent forms. But the forms also need to state clearly what the differences are in the outcomes that patients might care about. I argue that the intuition behind the variability of assessment of outcomes is at least partly what motivated many critics of the SUPPORT study into mistakenly asserting that the research was greater than minimal risk.

Just as research on informed consent in research has found inadequacies in participant understanding of basic facts about the research they are participating in, a great deal of research on clinical informed consent has demonstrated overwhelmingly that the quality of informed consent in the clinical setting is often very poor in practice. Physicians rarely meet standards of disclosure or of shared decision making. This problem should be recognized in considering the consent requirements for research within the standard of care. It clearly matters more in the cases where there is likely to be variation in assessment of the magnitude or severity of harm. Therefore in cases where, in the IRB's judgment, individual variation is likely, and there is any question that participants may not fully understand the trade-offs involved as a result of the standard informed consent process, it is reasonable for IRB's to require that a full discussion of the risks and benefits of clinical care for the treatment (as background) be included within the informed consent forms.

3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not?

Randomization in accordance with a protocol is not necessarily greater risk than clinical care. It may sometimes be the case that clinical judgment about very complex, known trade-offs between interventions will lead to individualized care that is beneficial over a protocol. But more typically, well-known and documented exogenous factors govern decision making by physicians when there are multiple options available, including geography, history, biography, advertising, and relationships with drug companies. In fact, physicians often tend to continue to practice in ways similar to their training even as evidence emerges that this is sub-optimal.

Opponents of this view have made several unsupported claims. In particular, they have argued that individualizing is always intrinsically better for patients than to be assigned based upon a protocol. Two important facts are worth noting in response. First, in some cases (as for example oxygen saturation targets in SUPPORT) standard clinical care is based upon on a protocol, not individual adjustment. Second, if there is no evidence to support the adjustments that are made, it is difficult to see how they can provide benefit.

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Opponents have also argued that because physicians have the patient's best interest as the primary goal (while researchers are aiming at producing generalizable knowledge) research is intrinsically riskier than clinical care. Again, there is little evidence to support this claim (see Faden, et al, Hastings Center Special Report, 2013, 43(1): S16).

Finally, the claim has been made that if there is a difference in what a patient receives (within the standard of care) as a result of randomization, this means that there is an increase in risk. This is explicitly stated in the OHRP letter of June 4, 2013 to UAB, in which it responded to critics and stated that the fact that participants in SUPPORT at many institutions used oxygen saturation targets that were different from what they normally would have used means that there was an increase in risk. This is false.

Suppose A and B are two drugs commonly used to treat a disease. Suppose also, there is no evidence to support using one drug versus another—they have similar known side-effects and it is not known if they occur more frequently with one versus another and it is unknown if one is more effective as a treatment that the other. Let us suppose though, that the company that makes A has a much larger marketing budget and as a result, 75% of physicians prescribe A, while only 25% prescribe B. Suppose a trial is designed in which participants are randomized to equal probabilities on a protocol of getting drug A or drug B. In this case, whether one is enrolled in research or getting clinical care, there will be a significant difference in the probability of what drug the person will receive. As a research participant, there is a 50% chance of getting A, while in clinical care, there is a 75% chance of getting A. But there is no difference in risk between enrolling in research and standard clinical care. In the absence of any basis for claiming that at the time of the trial that A or B is better, the expectation values are the same, whether one enrolls in research or a clinician uses her clinical judgment (informed by pharma marketing, other exogenous factors) to decide what drug to use.

In OHRP's letter, they correctly point out that infants in the study may well have targeted saturation levels that differ from what they would otherwise have received (and may have increased the chances of getting lower or higher levels within the standard target range of 85-95%). But at the time (and still today) there is no evidence to support the claim that it is better to allow infants to range across 85-95% than to be randomly assigned to a narrower range within that larger range. In short, the key is not whether the care will be different, but whether there is evidence that suggests that randomization will increase risk to participants versus those who will not be enrolled in research. If the answer to that is no, then the risk of enrollment is minimal—even if what a patient will receive is different from what they would otherwise have received. Not all research within standard of care is

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necessarily minimal risk—the question for the IRB is about comparing the expectation values of research versus standard practice.

Thank you for considering these comments,

Sincerely,

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PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 07, 2013
Status: Posted
Posted: August 08, 2013
Tracking No. 1jx-86wi-jl6e
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0014
Comment on FR Doc # 2013-15160

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General Comment

See attached file(s)

Attachments

OHRP CE research tyson Aug 7

HHS Public Meeting Regarding Research Assessing Standard of Care Interventions
August 28, 2013
Comments Submitted by Jon Tyson, John Lantos, Kathleen Kennedy, and Susan Wootton

*Our comments are focused on comparative effectiveness (**CE**) trials. CE trials compare outcomes for patients randomized to different treatment methods or management strategies used in clinical practice. CE trials differ from those for which current regulatory requirements for randomized trials were developed: trials comparing patients randomized to receive a new experimental intervention with control patients who receive conventional treatment or in some cases, a placebo or no treatment. The key difference is that CE trials have no "experimental" arm and no "control" arm and that the potential risks in one arm are the potential benefits of the other and vice versa.*

1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?

This question and others that follow would be clearer and more meaningful if the term "standard of care" was removed or carefully limited to therapies demonstrated to be beneficial (as judged by criteria like the GRADE criteria[1,2] or those of the U.S. Preventive Services Task Force[3]). This term causes confusion when applied to unproven but routinely or commonly used therapies or treatment strategies which unfortunately make up the great majority of therapies used in clinical practice.[4,5,6,7] The fact that most treatments fall in this category highlights the pressing need to promote CE trials and a learning health care system.[6,8,9,10] To call one treatment or another "standard of care" misrepresents the very problem that policies for oversight of CE trials must solve. Such therapies would be better described by terms like "usual care" or "conventional treatment."

The first step for IRBs is to ask "Is the proposed trial justified?" CE trials are justified when there is inadequate evidence to determine the best treatment method for the patients to be studied. This decision may not be easy and may well require expertise in the clinical issue under investigation or in study design or interpretation.[11]

The trial should be deemed justified when the best available evidence indicates no clear overall difference in the foreseeable risks (relative to the benefits) of the treatment methods to be studied. CE trials should not be performed if there already is strong evidence from a proper systematic review of prior randomized trials[12] (indicating that one of the therapies to be studied is superior to the other). Such evidence may not be recognized without this kind of review. An exception might be considered if a compelling argument could be made that evidence from prior trials may not be generalizable to current practice. In the absence of prior trials, the need for a CE trial should be challenged if a well done cohort study has identified evidence of either strong benefit or hazard (a relative risk for an adverse outcome that is either ≤ 0.10 or ≥ 10) for one treatment method to be studied relative to the other.[13] Otherwise, observational studies may be quite misleading and are usually an inadequate basis to conclude that a CE trial is unwarranted.

Therapies are ordinarily first evaluated in efficacy trials (to assess therapies under ideal or restricted circumstances). Therapies found to be beneficial in efficacy trials then need evaluation in effectiveness trials (to assess therapies in routine clinical circumstances). Therapies that are clearly beneficial but quite expensive may also be considered as appropriate for CE trials. In such situations, the trials would be designed to assess whether such therapies are reasonably cost effective for general use or limited use in highly selected centers or patient populations.

a. Under what circumstances should an IRB consider those to be risks that may result from the research?

The Common Rule states that the risks of research are the incremental risks from participation in research, as compared to the risks that would be experienced without study participation. In a legitimate CE trial the treatments under investigation are already used in clinical practice, and there is no predictable or reasonably foreseeable overall difference in their risks (relative to the benefits) as assessed from the best available evidence. So any differences in outcomes observed in the trial result from unpredictable treatment risks or baseline differences in disease severity and are not from the risks of the research itself.

Systematic reviews of outcomes for patients in well-designed RCTs provide no evidence that participation in a trial, compared to non-participation in the trial, increases the actual risks of adverse outcomes identified at the completion of the trial .[14,15] Thus, there is no empiric basis to assume that CE trials compromise the outcome of participants for the benefit of future patients. Physicians who conduct such trials are committed to the welfare of the patients. If they knew the best treatment for these patients, they would provide it. In some trials, patient risk may be reduced by the investigators' efforts to most effectively provide the therapies under investigation, to optimize the patient's supportive care and clinical monitoring, and to minimize and more quickly identify and address treatment hazards or disease complications than would occur in clinical practice.

b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?

As noted by OHRP, the IRB is to consider research risks to be only the risks and benefits that may result from the research (as distinguished from those that participants would incur even if not participating in research). In many studies, those risks are easily identifiable. They include risks from extra blood drawing, biopsies, or other procedures imposed by the study that would not ordinarily be done in routine clinical care. The IRB should consider these risks to be related to the research. They should not consider the risks of being assigned to one arm or the other of a CE trial to be a risk of research, even if, as a result of the study, the chances that a particular patient receives one therapy or another may be different if they are in the study compared to if they are not.

The specific risks of the individual therapies under investigation are likely to differ. However, the IRB's agreement that the trial is justified indicates agreement that there is no predictable overall difference in the foreseeable risks (relative to the benefits) of the treatment methods to be studied as judged from the best available evidence.

c. What type of evidence should an IRB evaluate in identifying these risks?

The IRB should evaluate the methodologically strongest relevant evidence in assessing the need for the trial and in identifying the specific risks of the individual therapies under investigation. The investigators should reference and describe the findings of any systematic review of all relevant randomized trials (particularly the well performed reviews of the Cochrane Collaboration). Unless refuted by rigorous randomized trials, evidence about treatment risks from well performed cohort or case-control studies may also be considered

Even in randomized trials, the available evidence is not always easily interpreted, particularly when the proposed trial involves populations or circumstances not previously assessed or when offsetting benefits and hazards or evidence of subgroup differences or treatment heterogeneity are identified in prior trials. As noted above, criteria like the GRADE criteria or those of the Preventive Task Force may help in evaluating and integrating the available evidence. The AGREE II criteria[16,17] may be helpful in evaluating the evidence underlying practice guidelines. IRBs, like investigators and clinicians, will need to stay abreast of methods being developed or used to evaluate when the treatment hazards outweigh the benefits for individual patients or patient subgroups.[18,19]

2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects?

a. What criteria should be used by the IRB to evaluate whether the risks to subjects are reasonably foreseeable?

We see a number of issues that should be considered for these questions:

A. The available evidence about potential treatment hazards. Potential risks that can be considered to be reasonably foreseeable would include a) biologically plausible treatment hazards that have not been well assessed in clinical studies, and b) hazards that have been evaluated in a systematic review of relevant clinical trials or in the absence of such a review, in one or more clinical trials or well performed cohort studies and found to marginally or significantly associated with the treatment ($p \leq 0.10$). In accordance with the principles of evidence-based medicine, investigators should not be required to list on a consent form all possible hazards or hazards that are not close to significant ($p > 0.10$) in systematic reviews or in well performed clinical trials or cohort studies. To deem such potential hazards as "reasonably foreseeable" would require investigators to list almost any hazard that that could be considered minimally plausible despite evidence to the contrary. This might more often mislead than inform potential research participants or their surrogates. Listing all potential minor or rare hazards would also distract attention from hazards of greater importance to patients.

Foreseeable treatment risks often do not include some or many of the secondary outcomes listed in the protocol. Investigators often specify exhaustive lists of secondary outcomes for CE trials to ensure that all potentially important outcomes are carefully monitored and recorded and that unexpected observed differences are accepted by reviewers as "pre-specified" outcomes. Whether these should be listed as risks hinges on the available evidence as noted above.

B. Risk disclosure with competing outcomes. From the public health perspective, the most important CE studies assess primary outcomes important to patients, e.g., heart attacks or strokes, rather than short-term changes in things like blood pressure or laboratory tests. Study participants often must be monitored for long periods of time to evaluate these outcomes. If the participants are at high risk for death, as would be the case for elderly adults or small premature infants, some or many may die before they have to opportunity to develop such outcomes. In this circumstance, death is thus a competing outcome that prevents the identification of other adverse outcomes. For this reason, it is often prudent to

include death in the primary outcome (e.g. heart attack, stroke, or death) even though the investigators may have no reason to think that the different treatments would result in a difference in mortality. Including death in the primary outcome can prove to be particularly fortunate if, as sometimes happens, one of the treatments under investigation is associated with an increased mortality rate despite reducing other adverse outcomes like heart attacks or strokes.[20] However, the inclusion of death in the primary outcome should not be assumed to indicate that a higher mortality is foreseeable based on the best available evidence or should be noted on the consent form as a foreseeable risk for either treatment group.

C. A need for individualized consent forms? It might be argued that incremental risks and benefits of study participation should be disclosed in comparison to the treatment that each individual participant would otherwise receive. However, this approach is unlikely to be feasible. Clinicians' treatment preferences often vary by provider, may be variable or change over time, and may not be known at enrollment. Efforts to individualize the consent form would lead to troublesome differences in the forms within and across different study sites. For these reasons, the risks and benefits of participation cannot be listed in separate "risks" and "benefits" sections of a typical consent form template. The "risks" of one study strategy (higher risk of xxx) are "benefits" (lower risk of xxx) for the other strategy. A better approach would be to inform subjects in a straightforward manner of the prevailing practice variation and explain why researchers believe that randomization is appropriate. This information would be the same for all subjects and would be consistent with the IRB's approval of the study as a legitimate CE trial.

4. The need to develop better and more uniform approaches to risk disclosure for use of unproven therapies in both research and clinical practice. This need requires further study of such issues as the wants, needs, and comprehension of patients (or their surrogates) in routine and emergent circumstances; the effects of differing approaches to risk disclosure (including nocebo effects[21]); and factors that can augment the validity of informed consent. It is difficult to see how any ethical principles including respect for persons, beneficence, or justice justify a different level of risk disclosure in clinical practice and clinical research for patients receiving the same unproven treatment method. There also seem to be no data to indicate that well informed patients support this double standard.

3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk?

Randomization should not be considered to increase risk in legitimate CE trials because:

A. As discussed above, randomization to alternative treatment methods in such trials has no foreseeable effect on treatment risks for participants in the trial.

Randomization is simply a tool to avoid differences in baseline risk between treatment groups that are a notorious cause of confounding in observational studies comparing different therapies. It thus reduces the possibility of misleading results and erroneous conclusions but has no effect on the risks of the treatments provided.

In many clinical circumstances, there is inadequate relevant evidence to determine which of a number of commonly used treatments is preferable. In those circumstances, the treatment that is chosen will depend on happenstance and vary as a result of such factors as where the patient happens to be treated, who the treating physician happens to be, and what his or her treatment preferences happen to be. Those treatment preferences may reflect the considerations of an extremely dedicated, well informed, and appropriately uncertain physician. Alternatively, it may be based on the physician's vague recall of the relevant research, a clinical anecdote, a casual conversation with colleagues, or a recent visit from a drug company representative. It may be a combination of these factors. The net result, in the absence of good evidence from good clinical trials, is a decision that at best is similar to a mental flip-of-the-coin

B. The unfounded assumption that clinical trials increase risk leads to associated regulatory requirements to warn patients of dubious or non-existent risks. This may inadvertently harm patients by disincentivizing proper testing in the most rigorous feasible CE research and by incentivizing clinical use of unproven and possibly hazardous therapies.

As indicated below, this effect can have major serious adverse consequences that should be carefully considered.

Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?

Providing the CE trial is justified, waiver would be allowable in some circumstances,[22,23,24,25] and well justified in urgent or emergent circumstances when valid consent cannot be reasonably obtained and when treatment delays to obtain consent (~ 1 hour, if not longer, in many trials) would be expected to alter the treatment benefits or hazards. This approach would expand the current criteria to allow waiver of consent when the treatment is not considered potentially life-saving and remove the requirement for community participation in these circumstances. Patients receiving proven emergency therapies benefit from prior studies, and their participation in well justified CE research are needed to further

improve outcomes. Requiring consent in these circumstance can A) increase the morbidity or mortality of trial participants;[26,27] B) result in erroneous conclusions that adversely affect the care and outcome of a very large number of future patients; C) delay completion of a valid trial and dissemination of truly beneficial therapies or abandonment of truly harmful therapies in clinical practice. Requiring consent in these circumstances violates the principle of beneficence and arguably, also respect for persons and justice.

Public understanding of CE research in these circumstances could be promoted by including potential study participants in the process of study design as well as by rigorous efforts to explain to participants who have been enrolled in trials of emergency therapies without their consent - in as timely manner as possible – the rationale for the study and the reasons why they or their loved one was enrolled. At that time, investigators should also seek the patient's consent to continue in the trial or to allow use of their data.

Whatever disclosure and consent procedures are required for CE trials, we would urge that they should be similar for all patients receiving the same unproven therapy whether as part of routine clinical care, a prospective observational study, or a randomized trial. As we have argued elsewhere,[29] consent procedures deserve reconsideration for clinical as well as research use of unproven therapies, particularly new unproven therapies. As Fost has emphasized, it is not plausible to presume that a patient would want a therapy never properly tested for safety or efficacy with no prior review, but would object to the same treatment being given with all the safeguards of a controlled trial. The current double standard for both risk disclosure and written consent inadvertently discourages proper testing, encourages clinical administration of unproven therapies, and contributes to the all-too-common problem that unproven therapies are widely used for years or even decades before they are rigorously evaluated and found to be ineffective or harmful.[5,28,29,30]

4. **How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions?**

The uncertainty about risk is influenced by the quality of the prior research, the p values and confidence intervals for the measures of treatment effect (relative risk, risk difference, and number needed to treat or number needed to harm), and in some studies, Bayesian estimates of the probability of specific treatment effects. The discussion above indicates how this uncertainty may be judged in addressing these questions. To the extent feasible, the level of uncertainty should be conveyed to study subjects, but optimal methods have not been developed for conveying these complex concepts to patients with variable skills in literacy and numeracy.

What if the risk significantly varies within the standard of care?

As noted above, the trial is not justified if the relationship of risks to benefits has been shown to be more favorable in one treatment group than the other(s). Suggestions are detailed above for disclosing risks and benefits or advantages and disadvantages of different study strategies that are within the range of common practice.

5. Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases risk of harm, or is it necessary that there be published studies identifying the risk?

It is unclear what is meant by "documented beliefs." However, the beliefs within the medical community about an intervention can vary widely, particularly if they have not been well assessed in randomized trials. As evident from the long unfortunate history of oxygen administration to premature infants,[31,32] the evidence supporting the treatment is more important than the level of belief among some or many physicians.

As noted above, potential treatment risks need not be disclosed if they were well assessed and shown to have no association in relevant clinical trials of these therapies, or in the absence of these trials, in well performed cohort studies. Biologically plausible potential treatment hazards that have not been assessed in clinical studies should ordinarily be disclosed if they would be of concern to a sizable proportion of patients.

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PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 07, 2013
Status: Posted
Posted: August 07, 2013
Tracking No. 1jx-86wf-k1l3
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0011
Comment on FR Doc # 2013-15160

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General Comment

Statement from Edward W. Campion, MD

Assessment of Risks of Standard of Care Interventions [Question #1]

The most pressing need in clinical medicine today is for rigorous clinical effectiveness research. This is research that is within what is currently accepted as the standard of care. Most of the decisions that physicians make in caring for patients are not based on evidence from randomized controlled trials or on other types of rigorous and extensive research data. From the clinic to the emergency room to the ICU, much of what is done every day relies upon a combination of a physician's personal clinical experience, what he or she was been taught by experts, and an understanding of physiology and disease, as well as upon local standards, expert recommendations, professional guidelines, point-of-care manuals, respected textbooks, and articles in the peer-reviewed literature.

We know that usual care varies widely depending on where you are. What may be standard medical practice in Miami is not seen as the 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, but the same types of variation can be seen in many aspects of care. And for

most of the regional variations in care, we don't really know which approach produces the best outcomes for patients. We can make progress here only through clinical effectiveness research on the different options that are seen as the usual standard. Often this means comparing an expensive newer intervention that is seen as an exciting advance with an intervention that has been around for many years. People may feel that one intervention is superior, but that view is not based on evidence.

Assessment of Potential Risks As Foreseeable [Question #5]

In assessing 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 should be established by data that document that the specific interventions are actually being used in situations and in a manner similar to those in the proposed research. Standard-of-care status can also be established from recommendations in relevant guidelines, clinical texts, point-of-care tools, and review articles in peer-reviewed journals. Once it is established that all the alternative interventions to be studied are recommended and in current clinical use and are seen as reasonably comparable and viable options, then randomization between them does not pose any additional risk. In these situations, the research itself poses no additional risk. Depending on the severity of the clinical problem and the nature of the intervention, there may 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 equivalent and within the standard of care.

What do patients need to know? First, if a patient is to be assigned to an intervention randomly, the patient needs to know about that random assignment and 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 the trial by speaking with the physician, reviewing the alternative interventions within the standard of care, and having their questions answered. Patients can also benefit from educational booklets or videos about their condition, the interventions, and the research project. And provision must be made for ongoing resources to answer any questions that patients may continue to have.

Once patients understand and agree to participate in standard of care research, they should be able to sign a simple consent form that is clear, short, and easily understood. Research that is genuinely within the standard of care should not be required to portray the risks of the alternative interventions as risks of the research. Those risks are inherent to the patient's condition or to the imperfect and under-studied interventions that are entirely within the current standard of care. It is misleading to patients, as well as harmful to the much-needed clinical effectiveness research, to describe those risks as deriving from the research itself. For standard of care research, long, legalistic consent forms that enumerate and catalogue all foreseeable risks do not help patients. In fact, they misleadingly communicate that the research itself is risky. The real risks come with the patient's condition and from the currently accepted interventions. And the risks to the patient are only made worse by the uncertainties that derive from insufficient research within the standard of care.

Submitted by:

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Docket HHS-OPHS-2013-0004

HHS PUBLIC MEETING ON APPLICATION OF REGULATORY REQUIREMENTS TO RESEARCH ON STANDARD OF CARE INTERVENTIONS

Statement

J. Michael McGinnis, M.D., M.P.P.

Date: August 7, 2013

Thank you for the opportunity to offer a comment in the course of a discussion of considerable importance to the vision and promise of continuous learning in health care. My name is Michael McGinnis, and I am Senior Scholar at the Institute of Medicine (IOM) of the National Academies. My statement is personal and descriptive in nature, and is not a statement or position of the Institute of Medicine or of the National Academies.

I would like to touch on 3 issues, each briefly:

- First, the impressive developments in the prospects and tools for continuous learning in health care, and the work of the IOM to accelerate progress;
- Second, the centrality of continuous learning from standard of care interventions as a conceptual and practical linchpin in capturing those prospects; and
- Third, the core implications of advances in science and technology in blurring traditional distinctions between research and practice—and the ability to assess outcomes and identify distinctions in real time.

Before getting to these three points, however, I would also like to underscore the IOM's long-standing interest in, and commitment to, the careful stewardship of research activities. In 2002, the IOM report *Responsible Research: A Systems Approach to Protecting Research Participants*, recommended uniform protection for all human participants in scientific research, as well as a refocusing of institutional review board (IRB) deliberations around the ethics of protecting research participants. In addition, and with increasing frequency, as with the 2009 report, *Beyond the HIPAA Privacy Rule,* IOM Committees have urged attention to the potential of regulatory impediments to inhibit the development of new insights from the care process and underscored the importance of practical adjustment to emerging opportunities for learning from and improving the safety and effectiveness of routine care.

Similarly, in 2012, the IOM Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs—a vein of research with some characteristics in common with standards of care interventions—called for a consent process tailored to the particular needs and risks of the post-market surveillance setting, including accommodation of issues of public health importance, absence of advantageous alternatives, and ability to monitor and respond to results. With this background of formal IOM assessments and careful stewardship of clinical research, I'll return to the three points characterizing my personal perspectives from our work on the continuously learning health care system.

The background to the first is clear, compelling, and well described in *Best Care at Lower Cost,* the report released last year by the IOM Committee on Continuously Learning Health Care in America. The Report summarized what we've learned about the implications of rapid increases in the complexity of care, the persistent harm and shortfalls in quality of care, and the 30 percent of 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.

At the same time, as the report 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. Fostering society's ability to capture this potential has been a major focus of the Institute of Medicine over the past several years. Through the IOM Roundtable on Value & Science-Driven Health Care, we have been working with colleagues throughout the field to map strategies for progress toward the vision of a continuously learning health system in which science, informatics, incentives, and culture are aligned for constant improvement and innovation. This vision, and its potential, is central to the discussions here.

To help marshal field leadership on the various dimensions important to realization of this vision, we have also formed several IOM Innovation Collaboratives to provide a venue for stakeholders to work together to foster change. One of these Collaboratives, the Clinical Effectiveness Research Innovation Collaborative (CERIC), is devoted to accelerating progress in continuous learning from the routine delivery of care. Several participants in that Collaborative, some here today, have put together a statement, to be introduced by Dr. Rich Platt, which does not represent an endorsed position by the IOM, but has grown out of discussions at Collaborative meetings.

An earlier example of such expert comments stemming from Collaborative discussions, and relevant for today's topic, is a 2011 discussion paper authored by certain CERIC participants: *The Common Rule and Continuous Improvement in Health Care*. In this paper, CERIC explored the role of risk in clinically-integrated research. The authors advocated for a risk-based framework in the application of human-subject research requirements, "in which oversight is commensurate with the level of risk imposed by the study." In such a framework, studies that impose little or no added risk to patients—such as those comparing routine interventions within the general standard of care—would not require IRB oversight. The authors concluded that focusing the regulatory environment on interventions that might present a discrepancy in the level of risk would both increase safety and lead to rapid expansion and acceleration in standard of care research. By extension, a risk-based regulatory framework could lead to a growing evidence base for the practices and procedures patients experience every day.

This raises the emphasis of my second point: the centrality of assessing standard of care interventions to the vision of the continuously learning health care system, in which every health care interaction is also an opportunity for learning and improvement. The notion of continuous quality improvement is not novel. It is standard practice in successful businesses, including the

practice of improving worker safety. In health care, with many variables in play, and variation in individual responses, improvement requires continuous monitoring 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 its early stages, it has already demonstrated its potential.

A 2013 discussion paper by members of CERIC, titled *Making the Case for Continuous Learning from Routinely Collected Data*, reviewed a wide variety of case studies illustrating the power of continuous learning to improve and accelerate care. In a high-profile example, the discovery that the popular arthritis drug Vioxx increased heart attack risk for certain users was accelerated in part by analyses of databases for routine care. On the public health front, the use of instantaneous data from EHRs enables much more precise—and even predictive—tracking of and intervention against epidemics. As my colleagues from CERIC will present in their statement, a recent CDC/AHRQ-supported standard of care study found that a set of three common, accepted practices for preventing hospital-acquired Staph infections exposed patients to significantly different levels of risk, leading to the suggestion of broad changes—and increased alignment—in practices for reducing the risk of hospital-acquired infections throughout the nation.

As to the third point, rapidly occurring advances in information technology, research methods, and tools for patient engagement have vast conceptual and practical implications for knowledge generation in health care. Implicit in this vision is the acknowledgement that research and practice can no longer be viewed as sharply discreet realms, but rather should be viewed as different areas in a continuous cycle of knowledge generation, application, and positive change. That is why this moment—this conversation about standards of care research and its associated policies and practices—is so central to the future of health progress.

As our knowledge generation capacities advance, it is true that, just as services within the standard of care will sometimes lead to unintended consequences and unexpected results, so will research evaluating those results reveal unintended consequences and unexpected results. But these anomalies, and their discovery, are far from the greatest risk facing our health care system today. As underscored in various IOM reports, far more significant is the risk to the health of our population as a whole from clinical care backed by judgment and tradition rather than a strong, growing foundation of clinical evidence. These circumstances are even more acute when near-life threatening conditions prevail. This challenge is harmful to patients and our nation as a whole, and we have at hand the tools to address it.

Also inherent in the notion of a continuously learning health system is the need to reconsider how information is provided about care choices, and about our regulatory approaches to the consent process. I won't go into this—you'll have ample commentary in that respect—but clearly we would be well-advised to give close attention to certain principles that may be operative: principles related to relative risk of options, the burden of the usual care experience,

accommodation of patient preferences, and participation in care decisions. Each of these is fundamental to continuously learning health care, as highlighted in *Best Care at Lower Cost.*

In summary, *Best Care at Lower Cost* outlined a path to continuous learning through generating and using real-time knowledge to improve outcomes; engaging patients, families, and communities; achieving and rewarding high-value care; and generating a new culture of care. Each of these relates directly to the issues facing HHS as it considers research on standard of care interventions. As HHS explores the details of policy change and application, a vital opportunity is presented to set the stage for the evolution of continuously learning health care that will substantially improve the ability of the health care system to not only protect and to treat, but to *promote* the quality and effectiveness of care yet to come.

PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 07, 2013
Status: Posted
Posted: August 08, 2013
Tracking No. 1jx-86wk-icol
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0018
Comment on FR Doc # 2013-15160

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General Comment

Please see attached document for statement.

Attachments

HHS standard of care interventions_Final

Statement on research studying standard of care interventions *

(HHS-OPHS-2013-0004)

The enclosed comments are meant to address Questions 1-4 in "Section III. Issues for Discussion" of the "Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions" published on pg 38343 in the Federal Register on June 26 2013.

Below is an index to allow for easy reference of the relevant page number and section of the paper that correspond to each question.

Question	Page number and section title addressing question
1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context? a. Under what circumstances should an IRB consider those to be risks that may result from the research? b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?	• Pg 3: Oversight calibrated to risk and patients expected role • Pg 4: Consent calibrated to patient expectations and risk • Pg 6: A new ethical framework • Pg 7: Rationalized, harmonized regulation regarding consent, collaboration, and dissemination of new knowledge • Pg 5: Redefine health care operations.
c. What type of evidence should an IRB evaluate in identifying these risks?	• Pg 3: Oversight calibrated to risk and patients expected role: • Pg 6: A new ethical framework • Pg 7: Rationalized, harmonized regulation regarding consent, collaboration, and dissemination of new knowledge • Pg 5: Redefine health care operations.
2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to	• Please see sections listed for Question 1

*** Individual authors are participants in the Institute of Medicine (IOM) Clinical Effectiveness Innovation Collaborative, from which the discussion stems. It does not represent a formal position of the IOM or the institutions of the authors.**

subjects? a. What criteria should be used by the IRB to evaluate whether the risks to subjects are reasonably foreseeable?	
3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk? Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?	• Pg 2: Intentional assignment of patients to different strategies • Pg 6: Regulation based on the full spectrum of risk:
4. How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions? What if the risk significantly varies within the standard of care?	• Pg 1: Introduction • Pg 4: Consent calibrated to patient expectations and risk

Introduction

The undersigned individuals offer these comments for the Department of Health and Human Services (HHS) public meeting on Federal policy regarding application of regulatory requirements for protection of human subjects to research studying standard of care interventions on August 28, 2013. Although we are all participants in the Institute of Medicine (IOM) Clinical Effectiveness Research Innovation Collaborative, which has engaged in active discussions on this issue, we emphasize that we offer these comments as our opinion and not that of the IOM.

We have all been closely involved in research policy issues in leadership positions and as researchers. We believe deeply in the potential for research to improve the quality of health care and the health of the nation. In our view, substantial changes are required in the regulatory framework of human research as it regards studies of routine clinical care. Changing our oversight approach to one that enables the broad learning now possible from routine health care can save many lives and prevent harm from widely used practices about which we lack sufficient information about absolute or relative effectiveness. We believe this can be done in a way that fully maintains our ethical and legal obligations to protect human subjects and the interests and rights of patients more broadly.

Current ethical and regulatory governance regimes under the Common Rule, the Health Insurance Portability and Accountability Act (HIPAA), and Food & Drug Administration (FDA) regulations were developed decades ago, when research and clinical practice were considered to be completely distinct activities[1]. There was little appreciation that clinical practice itself should be a subject of ongoing investigation to determine which practices produce the best health for which patients. Current regulations governing research, and their application in practice, create significant impediments to learning which of several accepted practices is superior. In part, this is due to the basic misconception that standard clinical practice has a settled evidence base. Instead, it is well documented that good evidence is often lacking and many standard medical practices are based on clinician judgment alone[2]. This often results in different treatments being used for identical indications, with clinicians and patients having no way to determine their comparative safety and effectiveness. There is thus great potential to improve patients' health outcomes through careful clinical evaluation to determine which currently accepted medical practices are best for which patients. But in order to gather knowledge that is critical to all patients, we need to change the view that research to learn what works is a completely separate activity from patient care. In fact, research to inform us about the best course of treatment must be done within the context of clinical practice to be applicable.

Research that compares prevention, diagnosis, and treatment strategies in common use is the essence of a learning health care system – one that continuously improves care, first by generating evidence as

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[1] Kass, N. E., Faden, R. R., Goodman, S. N., Pronovost, P., Tunis, S, and T. L. Beauchamp. 2013. The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight. *Hastings Center Report* 43(s1): s4-s15.

[2] Tricoci P., Allen J. M., Kramer J. M., Califf R. M., and S. C. Smith Jr. 2009. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 301:831-841

part of care delivery, and then applying this evidence in everyday practice[3]. Measurement, evaluation, systematic comparison of accepted therapies, sharing of experience and information, and coordination of these activities throughout the healthcare system should be normal expected activities. We focus here on studies of routine care that involve systematically modifying the care some patients receive, in order to understand the relative merits of two accepted approaches. The ethical and scientific basis of for this intentional assignment, or randomization, is the existence of clinical equipoise defined as "...a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm...[4]".

In considering the oversight of systematic research involving routine care, there are two critical components: 1) the intentional assignment of patients, either individually or in clusters, to one or another care approaches for the purpose of learning their relative effectiveness and safety, and 2) the use of patients' protected health information to support the evaluation. We first consider the use of protected health information in interventional research.

Use of protected health information: Under both the HIPAA Privacy rule and the Common Rule regulatory regimes, activities using identifiable data and falling under the definition of research, defined as those contributing to generalizable knowledge[5][6], are subject to more rigorous requirements than for treatment, payment and "health care operations." This includes IRB review in the case of the Common Rule, and prior consent or authorization of the data subjects (unless waived by the IRB – or in the case of the Privacy Rule, a Privacy Board).

Consequently, the same activity involving analysis of identifiable data is treated as routine, and subject to minimal regulatory oversight, as long as the analysis is intended to be used only internally. This approach, where more stringent review is required in circumstances where the results are intended to be shared with others, creates a disincentive to sharing the outcomes of quality and population-based analysis.

Intentional assignment of patients to different strategies: It is often possible to learn about the relative effectiveness of two approaches to care by using observational methods, comparing differences in policies or practices that organizations, providers, or patients choose for a variety of reasons. Much can also be learned from "quasi-experimental" situations, for instance when introduction of a new practice or policy permits assessment of changes over time.

However, in many situations the best, or sometimes only, way to draw any conclusion with confidence is to systematically assign some patients, practices, hospital wards, or health plans to different approaches (see example case study in the Appendix). A cornerstone of systematic assignment is some form of randomization to reduce the many potential differences that might otherwise be present between

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[3] IOM. 2007. *The Learning Healthcare System: Workshop series summary.* Washington, DC: The National Academies Press

[4] Freedman, B. 1987 Equipoise and the Ethics of Clinical Research. *N Engl J Med* 317:141-145.

[5] 45 CFR § 164.501 (2013).

[6] 45 CFR § 46.102(d) (2009).

groups. Sometimes this randomization can be as simple as determining by chance the order in which a new policy that must be implemented over an extended period is introduced to hospital units.

Although current regulations permit making such assignments without requiring informed consent under a set of constrained circumstances (including the determination of minimal risk and the impracticability of obtaining consent), they frequently impose additional hurdles regardless of how remote the topic is from the normal range of issues about which patients are engaged to make decisions. For example, decisions regarding several drugs in a class to include in a hospital's formulary or which type of soap a hospital uses for routine bathing in an intensive care unit.

Our recommendations to facilitate evaluation of practices in common use

A new regulatory regime for learning in health care is needed, along with guidance regarding implementation[7]. We will not attempt to lay out the contours of such a regime here, but we believe that doing so is essential and should commence as soon as possible. Here we articulate principles that could inform development of better guidance for implementation in the short term and a new framework in the long term.

Research as a routine component of care: Foremost, we should adopt the view that development of new knowledge should be woven into the delivery of healthcare. We should also eliminate the perverse incentives to degrade the quality of knowledge generation or dissemination in order to allow it to qualify for the less stringent oversight accorded to quality improvement activities or other operations decisions. We do not suggest that quality improvement programs or operations decisions require more oversight, or that all research should be overseen as quality improvement.

Oversight calibrated to risk and patients expected role: Oversight of studies of routine care should be based on the level of risk, either to the patient or to the misuse of their data, and to the patients' expected level of engagement in decision making in standard of care activities. Assessment of the risk imposed by studies of routine care should be of the "additional" risk imposed by the study as compared to regular care for that same situation. That is to say that oversight of a research study should depend on the risk imposed by the study, not the risk of the care situation, which would be the same even if the patient was not part of a systematic evaluation.

Use of patient data should be governed according to the risk of misuse and potential for harm, rather than whether or not the use is one that qualifies as routine "operations" (because the results will only be used internally).

Consent calibrated to patient expectations and risk: Similarly, informed consent beyond the general consent for treatment should not be required in instances where the decision between one intervention and another is one where the patient's input would not typically be sought (both because providers do

[7] Faden, R., Kass, N. E., Goodman, S. N., Pronovost, P., Tunis, S, and T. L. Beauchamp. 2013. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. *Hastings Center Report* 43(s1): s16-s27

not expect patients to be involved, and patients similarly do not expect to be involved), and where no appreciable additional risks are imposed compared to therapy in the absence of the research activity.

Research oversight and decision making should be transparent and should respect patients' rights to understand and participate in decisions about their care. However, we do not believe a complex individual consent process is required for every situation in which providers or health care systems perform a formal evaluation of routine operations. We believe this is true even if the evaluation involves randomization, particularly at the level of a practice, hospital ward, or health system.

In 1999 Truog et. al.[8] suggested that within certain criteria, consent for general care should be understood to provide authorization for participation in certain randomized studies. This view is consistent with the goals of a learning health system and the ethical framework and associated obligations described by Faden, et. al.[9]. Beyond the basic ethical requirements for trials such as equipoise, Truog's proposed criteria include considerations for whether the interventions assessed are outside what is covered under general consent for care, the risk/benefit profiles of the interventions being compared and how a reasonable person might be expected to interpret them, and the requirement that patients be informed that the institution uses these standards to guide consent requirements. These suggestions are consistent with limiting such studies to routine care in terms of risk and patient expectations, and addressing obligations to respect patient self determination through transparency, with opportunities for opting out as appropriate. These priorities can be applied to thinking about how to improve guidance within the current system of oversight and regulation and in designing a new one.

We also believe it is important to develop better evidence about what patients, the public, and other stakeholders expect of the health care system and their providers, with respect to oversight of studies of routine care and the role of consent. A program of empirical research to gain a better understanding of expectations and to test approaches will help guide development and implementation of revised regulations.

Enable coordination: There should be no barrier to coordination between organizations' working in concert with one another, such coordination is necessary to address many important problems, as the example in the appendix shows.

Encourage dissemination: Widespread dissemination of new knowledge arising from any activity is essential to improving health care. Sharing of results does not itself trigger additional privacy risks for individuals, if the results are reported in a way that adequately protects the identity of persons in the study and care is taken to avoid risk of stigma to subpopulations.

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[8] Truog, R. D., Robinson, W., Randolph, A., and A. Morris. 1999. Is informed consent always necessary for randomized, controlled trials? *New England Journal of Medicine* 340 (10): 804–807

[9] Faden, R., R., Kass, N. E., Goodman, S. N., Pronovost, P., Tunis, S, and T. L. Beauchamp. 2013. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. *Hastings Center Report* 43(s1): s16-s27

Actions within the current regulatory regime

Some progress in improving the oversight of studies of routine care is possible without changes in regulation. A basis for the development of such guidance could be a greater reliance on the kind of comprehensive risk spectrum discussed previously. One example of how this could be applied is including consideration of whether an evaluation introduces additional risk not already covered by other regulations, such as HIPAA oversight of personal health information disclosure risk, in assessing the need for additional consent beyond consent for care.

To make the fullest possible use of the existing regulations, OHRP, the Office of Civil Rights, and the FDA should provide more complete and coordinated (to the greatest extent possible) guidance about activities that are permitted under existing regulation. This could be done through the development of guidance that explicate the range of permitted activities, as well as developing annotated "case-law" descriptions of evaluations of standard of care interventions that demonstrate acceptable application of existing regulations. Establishing precedents through this and other means will help IRBs and Privacy Boards to avoid making unnecessarily restrictive decisions because of uncertainty about what the regulations allow.

Redefine health care operations. One option for working within the current regulatory framework is to broaden the definition of health care operations as it is used in the context of HIPAA and the application of the Common Rule. In the context of a learning health system, systematic assessment of operations should be a routine part of operations. To some extent the rules already allow for this by including quality improvement activities as operations. However, as already noted, the use of rigorous, systematic methods in quality improvement often leads to its reclassification as research subject to HIPAA and the Common Rule research provisions. Avoiding this reclassification, unless it is accompanied by an increase in risk would be a short term solution to facilitating these assessments. However, any new guidance clarifying that certain assessments of interventions would not be considered "research" for purposes of these regulatory regimes must recognize that such assessments will generate new knowledge and dissemination of findings through publication and other means. Oversight of such activities would be the responsibility of organizational processes other than IRBs and Privacy Boards, building on processes that are already in place to govern routine care and quality improvement. This expansion should include operations activities that use FDA regulated products assuming they are approved and in general use.

Risk-based approach to regulating data: In some respects, the Common Rule and the HIPAA Privacy Rule do regulate research on data based on risks to privacy and confidentiality. For example, neither regulatory regime regulates the use of data that is not at risk (or raises very low risk) of being identifiable to a particular patient. In addition, the HIPAA Privacy Rule allows a "limited data set" (data that excludes 18 categories of common identifiers) to be used for research purposes without the need for prior consent or authorization of patient data subjects.[10] More consistent application of risk-based standards and principles to guide regulation of research uses of data will result in greater protections for

[10] The Health Insurance Portability and Accountability Act of 1996 (HIPAA; Pub.L. 104–191, 110 Stat. 1936, enacted August 21, 1996)

patients, because more stringent regulation will be targeted to those activities with the potential for harm, and ease the regulatory burden on those activities that can contribute to the learning health care system without increasing risks to patients.

In cases where IRB review is necessary, guidance for IRBs should include consideration of the level of risk to the privacy and confidentiality of identifiable patient data and support waiver of consent requirements in circumstances where the privacy and confidentiality risks are also low. Among the factors that should be considered are the following:

- Does the study increase the risk of exposure of sensitive, identifiable data?
- Does the study involve identifiable data being accessed by outside entities/third parties?
- Does the study include other features that increase the potential risks to privacy and confidentiality?

We support efforts to realign the Common Rule and other relevant regulations so that they regulate less stringently those activities that introduce minimal risks for patients, both from a privacy perspective as well as an intervention perspective. The above criteria could also be used by institutions to determine whether additional review is required by an IRB or Privacy Board in a circumstance where data are being collected to study treatments already in common practice. In addition, we urge HHS to work with stakeholders to more clearly define the aspects of research that introduce risk (both from a privacy and interventional standpoint) and focus on tailoring regulation to more appropriately address those risks.

Regulation based on the full spectrum of risk: Following on our call for a more risk-based approach to oversight of studies of routine care, full characterization of the risk to patients in the context of care is important. This includes the fact that routine care carries risk. The risk of routine care is often very high, both because of the limits of what is currently available to treat certain illness and injuries and because of medical errors and other failures to deliver quality care. At present, this risk is exacerbated by the fact that many medical decisions are made without a strong evidence base, especially regarding the relative merits of two seemingly equal approaches. We believe that providing care without learning what works best increases the risk of subjecting patients to treatments that will not help them and could even hurt them. Consideration of patients' total risk, and how it fits into the kinds of decisions that patients usually cede to their clinicians, is important to assessing whether a research activity conveys additional or more than minimal risk.

New and reformed regulations

Ultimately, new regulation of assessments of routine care will be needed to support a continuously learning health system. These new regulations should be developed in consultation with all relevant stakeholders including front line clinicians, researchers, bioethicists, and patients.

A new ethical framework: A new ethics framework that includes responsibility to learn and improve as part of health care is needed to ground this new approach to governance of studies of routine care. Faden et. al. lay out such a construct in their recent paper An Ethics Framework for a Learning Health

Care System[11]. This framework "rejects the assumption that clinical research and clinical practice are fundamentally different enterprises" and suggests that all stakeholders share a moral obligation to contribute to learning and the improvement of health care.

This ethical framework suggests that a new regulatory regime should refocus oversight and consent on specific characteristics or features of learning activities. This is in contrast to the current approaches that rely on the motivation for the activity, such as whether the results will contribute to generalizable knowledge and be widely disseminated. As has been discussed before, risk, both physical and informational would be a characteristic key to assessing the appropriateness of in this approach. Additional factors include whether an intervention involves treatments in common practice, and the existing level of evidence for their use; whether the type of intervention is one that is typically discussed with patients in the context of shared decision making; and whether the proposed analyses rely on routinely collected data versus require the patient's involvement in the collection of additional data.

Rationalized, harmonized regulation regarding consent, collaboration, and dissemination of new knowledge: The regulations of all HHS agencies, including the Office of Human Research Protection, the Office of Civil Rights, and the Food and Drug Administration, covering research on therapies in common use should be harmonized to the greatest extent possible. New regulation should broaden the situations in which informed consent can be waived for investigations that assess standard of care prevention, diagnosis, or treatment regimens. The regulations should specifically allow for waiver of consent both for randomization of individuals, and also cluster randomization as a method of evaluating policies and practices that organizations such as hospitals might otherwise introduce without any rigorous evaluation. Further, the regulations should impose no barriers on collaborations between organizations to accelerate understanding of best practices, or to widespread dissemination of findings.

[Please see following pages for list of signatories]

[11] Faden, R., R., Kass, N. E., Goodman, S. N., Pronovost, P., Tunis, S, and T. L. Beauchamp. 2013. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. *Hastings Center Report* 43(s1): s16-s27

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Professor of Internal Medicine and Health Management and Policy
Director, Institute for Clinical and Translational Science
University of Iowa

Richard L. Schilsky, MD, FACP, FASCO
Chief Medical Officer
American Society of Clinical Oncology

Kevin A. Schulman, MD
Professor of Medicine and Gregory Mario and Jeremy Mario Professor of Business Administration
Associate Director, Duke Clinical Research Institute
Duke University

J. Sanford Schwartz, MD
Leon Hess Professor of Medicine and Health Management & Economics
University of Pennsylvania

Joe V. Selby, MD, MPH
Executive Director
Patient-Centered Outcomes Research Institute

Gregory Simon, MD, MPH
Senior Investigator
Group Health Research Institute

Jeremy Sugarman, MD, MPH, MA
Harvey M. Meyerhoff Professor of Bioethics and Medicine
Johns Hopkins Berman Institute of Bioethics

Christine M. Weston, PhD
Assistant Scientist
Center for Health Services and Outcomes Research
Johns Hopkins Bloomberg School of Public Health

Mary Woolley
President and CEO
Research!America

Albert W. Wu, MD, MPH
Professor and Director
Center for Health Services and Outcomes Research
Johns Hopkins Bloomberg School of Public Health

Mone Zaidi, MD, PhD, MBA, FRCP
Professor of Medicine and of Geriatrics
Mount Sinai School of Medicine

Appendix: An example of research in the learning health system

The study: A recent study sponsored by the Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality evaluated the effectiveness of three methods currently in routine use for preventing hospital-acquired infections in patients cared for in intensive care units.[12] These infections are among the most important preventable complications of medical care. The methods tested were 1) screening of patients for carriage of methicillin-resistant *Staphylococcus aureus* (MRSA), and use of isolation precautions for patients found to be carriers, 2) screening, isolation, and addition of a topical regimen to remove MRSA, which consisted of bathing of these carriers with soap containing the over-the-counter antiseptic chlorhexidine, and applying an antimicrobial ointment, mupirocin, in the nose, and 3) discontinuing screening and using the topical regimen for every ICU patient.

The study used a cluster randomized design in which 43 Hospital Corporation of America (HCA) hospitals that volunteered to participate were randomized to one of the three methods. Standardized infection control policies for HCA facilities are set at the corporate level and organizational leadership was motivated to identify the optimal approach through systematic research. For any particular hospital, every patient in its adult ICUs was treated the same way. There were several reasons for using cluster randomization. Two of the most important were 1) the desire to evaluate the performance of these three methods under conditions of actual use, which is possible only if the entire ICU follows the same standard operating procedure, and 2) the need to treat all patients identically because patients who are carriers of pathogens can transmit them to others in the same ICU.

The study ultimately involved over 70,000 patients. It found that discontinuation of screening and use of universal decolonization resulted in a significant reduction in the burden of MRSA and in the bloodstream infections due to any cause. An accompanying editorial, "Screening Inpatients for MRSA – Case closed," concluded that screening, currently mandated by several states, should be discontinued.[13]

Questions the study raised about ethical and regulatory oversight:

- Could individual informed consent be waived?
- How should FDA regulations be applied to comparative effectiveness research?
- Does randomization alter the determination of minimal risk?
- How could the study address the special provisions governing research involving prisoners?

The Institutional Review Board reviewing for a majority of the hospitals where the research was conducted under an Institutional Authorization Agreement (IAA) determined that the protocol met the criteria for waiver of individual informed consent: the research was determined to involve not more

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[12] Huang, S. S., Septimus, E., Kleinman, K., Moody, J., Hickok, J., Avery, T. R., Lankiewicz, J., Gombosev, A., Terpstra, L., Hartford, F., Hayden, M. K., Jernigan, J. A., Weinstein, R. A., Fraser, V. J., Haffenreffer, K., Cui, E., Kaganov, R. E., Lolans, K., Perlin, J. B., Platt, R.; CDC Prevention Epicenters Program; AHRQ DECIDE Network and Healthcare-Associated Infections Program. 2013. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 368(24): 2255-2265

[13] Edmond, M. B., and R. P. Wenzel. (2013). Screening inpatients for MRSA–case closed. *N Engl J Med*368(24): 2314-2315

than minimal risk to subjects; the waiver would not adversely affect their rights and welfare, as the intervention was similar to care provided in non-research situations and only de-identified information would be disseminated; and the study could not practicably be performed if individual consent were required.

Although the study was designed to evaluate the effectiveness of three widely used strategies to prevent MRSA in hospital ICUs, because some of these strategies involved the use of FDA regulated products (chlorhexidine cloths and mupirocin), FDA's regulations were also applied (21 CFR 312.3, 56.109 (c)(1). FDA's regulations have no provision for waiver of consent. Therefore, this study's lead IRB did require consent. However, as the research met the regulatory requirements under 56.109(c)(1), the IRB waived documentation of consent, as the research presented minimal risk and, as a quality improvement initiative, would not normally require individual consent outside of the research context and a modified consent process. Documentation about the hospital's quality improvement initiative was to be posted in ICU rooms and in admission materials. The notice contained the elements required for consent to participate in a research study.

Also at issue was the use of disposable cloths impregnated with chlorhexidine. These cloths were FDA approved for bathing use before surgery, but there was no specific approval to use them for routine bathing of ICU patients. The question was raised whether an Investigational New Drug license (IND) was required. The IRB concurred that an IND was not required as the regulated product was being used in the manner for which it was approved (bathing), and was not intended to support an application for a new use or marketing of the product.

DHHS regulations require additional safeguards for the protection of prisoners in research. These safeguards are found in 45 CFR 46, Subpart C. Subpart C applies to all research that includes any individual who is or becomes a prisoner while participating in a research study. Many IRBs—including the IRB for this study— are not authorized to approve research involving prisoners as they do not have a qualified prisoner representative as part of their membership, which is required by DHHS regulations. This was important because it was possible that some prisoners might be included in the tens of thousands of patients hospitalized during the course of the study. There was no effective method for excluding prisoners from the research protocol, since hospitals used their assigned regimen for all of their patients. Nor would it have been possible for hospitals to avoid admitting prisoners for the duration of the study. The problem could be addressed in this study because one of the participating hospitals' IRBs had a qualified prisoner representative, and was able to conduct a review on which the other participating IRB's could rely.

Discussion: Any hospital in a state that did not mandate screening could have adopted any of these approaches as its standard practice. Hospitals routinely implement these types of strategies without consulting or informing their patients. Hospitals typically do not ask individual patients to consent to bathing or isolation procedures. Any hospital could have compared these strategies as part of a Quality Improvement program. However, no single hospital is large enough to answer the important question at issue. Current quality improvement guidelines make no provision for hospitals to work in concert to answer a question that is important to all of them. Despite recent OHRP guidance, in many settings,

publication of findings, which is often critical to ensuring that what is learned results in significant impact, triggers the Common Rule's "generalizable new knowledge" criterion that is a distinguishing feature of research.

Although this study's lead IRB determined that the study satisfied the non-FDA criteria for waiver of consent, other IRBs have concluded that studies similar to this one did require individual consent, effectively precluding such studies. Some IRBs would not have considered posting of a notice on the wall of patients' rooms to be sufficient. Some IRBs would have required the investigators to apply for an IND, a requirement that makes many studies infeasible. Finally, this study had the simple good fortune that one of the 43 participating hospitals' IRB was able to review protocols involving prisoners.

PUBLIC SUBMISSION

As of: August 08, 2013
Received: August 06, 2013
Status: Posted
Posted: August 07, 2013
Tracking No. 1jx-86vx-zlfa
Comments Due: September 09, 2013
Submission Type: Web

Docket: HHS-OPHS-2013-0004
HHS Public Meeting Regarding Application of Regulatory Requirements at 45 CFR Part 46 to Research Studying Standard of Care Interventions

Comment On: HHS-OPHS-2013-0004-0001
Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

Document: HHS-OPHS-2013-0004-0010
Comment on FR Doc # 2013-15160

Submitter Information

Name: Ann C. Bonham, Ph.D.
Address: 20037
Email: hpierce@aamc.org
Organization: Association of American Medical Colleges

General Comment

Attached, please find comments of the Association of American Medical Colleges on matters related to the protection of human subjects and research studying standard of care.

Attachments

HHP OHRP Comment Letter SUPPORT Aug 6

Association of American Medical Colleges
2450 N Street, N.W., Washington, D.C. 20037-1127
T 202 828 0400 F 202 828 1125
www.aamc.org

Aug. 6, 2013

Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Submitted to www.regulations.gov

RE: Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions, 78 FR 38343, Docket number HHS-OPHS-2013-0004

The Association of American Medical Colleges (AAMC) welcomes the opportunity to respond to the above-referenced notice and request for comments from the Department of Health and Human Services (HHS) and Office for Human Research Protections (OHRP) on matters related research studying standard of care interventions. The AAMC is a not-for-profit association representing all 141 accredited U.S. and 17 accredited Canadian medical schools; nearly 400 major teaching hospitals and health systems, including 51 Department of Veterans Affairs medical centers; and 90 academic and scientific societies. Through these institutions and organizations, the AAMC represents 128,000 faculty members, 75,000 medical students, and 110,000 resident physicians.

The AAMC is pleased that OHRP is engaging the broad research, clinical, and bioethics community to respond to the complex issues that arose in the context of the SUPPORT study. We are concerned that the controversy significantly and unnecessarily damaged the public's trust in the commitment of physicians and scientists to protecting human research subjects, especially those in high-risk populations.

We underscore the critical need for empirical research to refine the "standard of care" and clarify the definition of reasonable foreseeable risk and provide informative and reasonable guidelines for disclosure of those risks. We urge HHS and OHRP to undertake a process for providing guidance that supports and facilitates comparative effectiveness research to determine efficacy and safety. The OHRP actions and subsequent controversy in response to the SUPPORT study has created a chilling environment for clinical research, and may essentially discourage future clinician researchers from engaging in rigorous research to generate evidence for the best possible treatments for critically ill patients, leaving physicians in the difficult position of making clinical judgments on a case-by-case basis. This will be a disservice to future patients and to the public.

At the heart of the SUPPORT-study controversy are the questions of the definition of reasonable foreseeable risks; who defines reasonably foreseeable risks; and what information about reasonably foreseeable risks should be included in an IRB's considerations and in informed consent documents when subjects are randomized to one or more standard of care interventions.

How Should the IRB Assess Risks of Standard of Care Interventions?

As a general principle, decisions related to proposed research on standard of care; identifying and communicating risks to subjects; and how standard of care, the progression of the underlying disease, and randomization procedures are assessed in terms of research risks are important questions and should be addressed within the framework for IRB review. The assessment of whether a risk is potential or known should be based on information available to the principal investigators, regardless of whether the research focuses on standard of care or a less tested intervention.

An IRB should consider the best currently available evidence (which may come from empirical research, past clinical experiences, general practice guidelines and consensus documents) for assessing risks of research on standard of care interventions.

1. Expected or likely outcomes inherent to the progression of the disease, given the subject population, and risks associated with all known standard of care interventions should *not* be conflated with the risks of participating in the research itself. It is critical to distinguish for both the IRB and potential research subjects the risks that may be inherent to the condition or disease state and to the standard of care treatment from the risks of participating in research. As an example from the SUPPORT trial, the risks involved in the standard of care interventions were potentially conflated with the high potential for a poor outcome given the high mortality rates in the subject population of severely premature infants. Of note, the infants in both arms of SUPPORT had a lower death rate than a similar group of infants in the Neonatal Research Network on whom mortality rate statistics were collected at the same time.

2. When the relative risks of the standard of care interventions are unknown, those variations in risks should not generally be considered by the IRB as a risk of the research.

3. When an identified risk is common to one or more standard of care interventions, an IRB should not consider that risk as a risk that may result from the research itself.

What Factors should the IRB Consider in the Identification and Disclosure of Reasonably Foreseeable Risks: Differentiating Underlying Disease from Risks of Interventions and Risks of Participating in Research?

1. IRBs should have clear guidance to help determine their assessment of reasonably foreseeable risks that must be disclosed to research subjects; the nonbinding guidance should be based on the risks of participating in the research itself and on the best information that is available at the time the research is proposed. Guidance should clearly establish what is permitted under the current regulations. When IRBs perceive new guidance as creating additional "extra-regulatory" restrictions on research, this can lead to interpretations of the regulations that are more restrictive than necessary.

2. Factors guiding IRB decisions in identifying and disclosing risks of standard of care interventions should include whether an intervention involves treatments in common practice and whether the *choice of intervention is one that is typically discussed with patients*, rather than whether or not the patients are part of a research protocol.

3. The adequacy of an informed consent document should *not* be assessed based on a retrospective evaluation of the results of the research. The fact that a research study concluded that one intervention was more effective or had better outcomes than another should not necessarily indicate that subjects should have been informed in advance about the potential for those differences. Such approaches fundamentally damage the public's trust in the protections that our institutions provide to the volunteer research subjects who are so vital to advancing learning and new knowledge.

4. The IRB should also have guidance to help them assess whether the difference in known risks and benefits of two standard of care interventions are so sufficiently documented or proven that the research itself is unethical and efforts should be directed at a national effort to revise the standard of care. In research like the SUPPORT study, where there is no consensus in the relevant field that one intervention (or narrow array of options in a wide range of currently acceptable values) is preferable over another, the likely variation in outcomes is the fundamental purpose of the study, not a risk of participating in the research. As with research that does not involve standard of care interventions, if the outcomes of the study are entirely predictable before embarking on the study, this raises the question of whether the research should be undertaken at all.

Too often, the undiscussed risk of standard of care treatment for a patient is that a physician has no solid evidence on which to base a recommendation of one intervention over another. Uncertainty about the risks of various standard of care interventions is often the driving force behind conducting a study, and necessitates the research.

Risks of Randomization Procedures

There is not one uniform standard that should apply to all proposed studies with regard to whether randomization is an additional risk that should be disclosed or simply a procedural element in the description of the study.

1. Randomization itself should not be automatically considered a risk to the subjects, especially in those cases where knowledge of the differences in risk or efficacy between the interventions leaves providers with little rationale to make clinical decisions about which to recommend. In other words, when clinical care decisions are routinely made in a way that is essentially no different than randomization to different interventions, research that incorporates randomization may not pose any additional risk to subjects.

2. If the relative risks between two interventions are thought to be nominal (as in the case, perhaps, where there are few known differences between two standard of care interventions other than a significantly higher cost of one over the other) or when exclusion criteria eliminate individuals for whom one intervention is clearly indicated over another, then randomization still poses no more than minimal risk.

OHRP Should Facilitate Comparative Effectiveness Research on Standard of Care Interventions through Guidance and Actions

If OHRP, with input from clinicians, researchers, patients, ethicists and other stakeholders, developed a suggested process and guidance for IRBs to follow when assessing proposals for research on standard of care interventions, this would benefit the community and public as a whole. Guidance could be provided to IRBs on both the criteria for approval and informed consent requirements for research on standard of care. As important as this information is, HHS and OHRP must take a strong position on the importance of such research as a learning or knowledge generating activity, rather than considering whether the activity is routine care, or "research." Robust scientific study—including learning and knowledge generation on current clinical care decision-making—strengthens our healthcare delivery system and improves the health of all. The government should be facilitating, not impeding the learning and knowledge that comes from this research.

Without essential research like that represented by the SUPPORT study, physicians are forced to use anecdotal information or rely on the customs that they learned as trainees to make clinical decisions. Recent federal commitment to patient-centered outcomes research and comparative effectiveness research has been welcomed by the medical and research community. At a time when scientists are sorely needed to conduct research to determine what works best for whom and why we must work diligently to ensure that we do not create an environment that discourages the learning and knowledge from such research.

Physician scientists could reasonably decide that going with their clinical judgment even without strong evidence may be preferable to facing professional and personal risk in trying to obtain the best evidence. Even the most dedicated physician scientist may think twice before heading into the debris left by the public condemnation of the SUPPORT study, which called into question the ethics of the government and the investigators. In the end, that hesitation could bring comparative effectiveness research to a grinding halt, leaving physicians in the untenable position of taking a reasonable guess, instead of ensuring that all patients receive treatment based on the best possible evidence.

The AAMC is again grateful to HHS and OHRP for this opportunity to comment, and we look forward to participating in ongoing discussions about these matters. Please contact me or Heather Pierce, J.D., M.P.H., Senior Director for Science Policy and Regulatory Counsel at hpierce@aamc.org with any questions about these comments or if the AAMC can be of any assistance during this important inquiry.

Sincerely,

Ann C. Bonham, Ph.D.
AAMC Chief Scientific Officer

Gordon, Valery (NIH/OD) [E]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Wednesday, August 07, 2013 2:55 PM
To: Carr, Sarah (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]
Subject: FW: Support meeting
Attachments: HHS Public Meeting_Amended FR Notice 2013-19056.pdf

Fyi -

Notice from HHS that we might group commenters on theme depending on how the comments look -- as opposed to the original plan of 1st come 1st serve.

-----Original Message-----
From: Abel, Kathy (NIH/OD) [E]
Sent: Wednesday, August 07, 2013 9:47 AM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Support meeting

-----Original Message-----
From: StithColeman, Irene E (HHS/OASH)
Sent: Wednesday, August 07, 2013 9:43 AM
To: Lewis, Caya (HHS/IOS); Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC)
Cc: Koh, Howard (HHS/OASH); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); LaPan, Jarel (HHS/IOS)
Subject: RE: Support meeting

The amended Support meeting FR published in today's Federal Register.

Irene

-----Original Message-----
From: Lewis, Caya (HHS/IOS)
Sent: Wednesday, July 24, 2013 4:45 PM
To: Menikoff, Jerry (HHS/OASH); Dotzel, Peggy (HHS/OGC)
Cc: Koh, Howard (HHS/OASH); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); LaPan, Jarel (HHS/IOS); StithColeman, Irene E (HHS/OASH)
Subject: RE: Support meeting

Thanks Jerry.

-----Original Message-----
From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, July 24, 2013 2:55 PM
To: Dotzel, Peggy (HHS/OGC)

Cc: Koh, Howard (HHS/OASH); Lewis, Caya (HHS/IOS); Horowitz, David (HHS/OGC); Palm, Andrea (HHS/IOS); Corr, Bill (HHS/IOS); Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); LaPan, Jarel (HHS/IOS); StithColeman, Irene E (HHS/OASH)
Subject: RE: Support meeting

Peggy,

Our thanks to you and Laura for putting this together. And yes, OHRP will go ahead and get this published.

Jerry

-----Original Message-----

(b)(5)

Gordon, Valery (NIH/OD) [E]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Friday, July 26, 2013 6:59 PM
To: Carr, Sarah (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]
Subject: FW: Support meeting
Attachments: FR Notice clarification SUPPORT public meeting.doc

This is a great step!

-----Original Message-----
From: Abel, Kathy (NIH/OD) [E]
Sent: Wednesday, July 24, 2013 3:01 PM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: Support meeting

(b)(5)

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Porter, Kevin (NIH/OD) [E]

From: Lusi, Rose (HHS/OS)
Sent: Tuesday, July 23, 2013 3:20 PM
To: Collins, Francis (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]
Subject: From Andrea - for support meeting in progress
Attachments: support study meeting .pdf

Categories: Important

-----Original Message-----
From: Lusi, Rose (HHS/OS)
Sent: Tuesday, July 23, 2013 3:18 PM
To: Lusi, Rose (HHS/OS)
Subject: Scanned document from Lusi, Rose (HHS/OS) (rose.lusi@HHS.GOV)

August 28, 2013 HHS Public Meeting
On Matters Related to Protection of Human Subjects and Research Considering Standard of Care Interventions
9 am-5 pm in the HHH Great Hall

Panel composition

- Strongly recommend that no "politicals" serve on panel to avoid the appearance of political bias.
- Dr. Wanda Jones, Principal Deputy Assistant Secretary for Health, to serve as moderator (State purpose of meeting, introduce speakers, serve as "traffic cop" to keep speakers/meeting running on time.)
- OHRP representative – Jerry Menikoff, MD, JD, OHRP Director.
- NIH representative, to be recommended by NIH.
- FDA representative, to be recommended by FDA.

Meeting Format

- Majority of meeting reserved for comments from registered presenters.
- As per the Federal Register notice, only panel members may question presenters.
- Time allotted for each presentation will be determined by HHS, based on the number of registered presenters.
- As per the Federal Register notice, presenters will be scheduled to speak in the order in which they registered to speak.
- Facilities will provide red/yellow/green light to maintain time limit of presentations.
- Public comments that have been submitted in advance of the meeting will be available online. In addition, one or two notebooks containing copies of the submitted comments will be available on-site for meeting attendees to view.

Important Deadlines (articulated in Federal Register notice)

- Registration to attend the meeting (but not to present) is 5 pm, Aug. 14.
- Registration to present at the meeting is 5 pm, Aug. 7.
- Deadline for submitting written comments for discussion at the meeting is 5 pm, Aug. 7.
- Deadline for submitting comments after public meeting is 5 pm, Sept. 9.
- Presenters will be contacted prior to the meeting to be notified of their approximate presentation times. They will be asked to submit copies of their presentations beforehand, to be identified with docket number HHS-OHRP-2013-0004, to http://www.regulations.gov

Number of Registrants as of COB Thursday, July 23, 2013

- 130 registered to attend and/or present
- 20 registered to present (2 are NIH employees)
- 110 registered to attend, but not to present

Bartok, Lauren (NIH/OD) [C]

From: Houser, Anne (NIH/OD) [E]
Sent: Tuesday, July 23, 2013 10:37 AM
To: Hudson, Kathy (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; White, Pat (NIH/OD) [E]
Cc: Houser, Anne (NIH/OD) [E]
Subject: FW: SUPPORT Clinical Trial QFR
Attachments: SUPPORT Clinical Trial.docx

From: McGrath, Jason (OS/BPER)
Sent: Tuesday, July 23, 2013 10:31 AM
To: Houser, Anne (NIH/OD) [E]
Cc: Gannon, Jennifer (HHS/ASFR)
Subject: SUPPORT Clinical Trial QFR

Hi Anne,

The attached response to the SUPPORT Clinical Trial QFR has been agreed to by NIH and OASH. We've sent this to the Subcommittee.

Thanks,
Jason

Jason McGrath
Office of the Assistant Secretary for Financial Resources
Department of Health and Human Services
(202) 690-6704

SUPPORT Clinical Trial

The University of Alabama at Birmingham (UAB) recently received a letter from the Office for Human Research Protections (OHRP) about the SUPPORT clinical trial, a research study of premature infants and supplemental oxygen. In the letter, OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study.

1. Could you please provide the specific scientific data that existed at the start of the study that shows this increased risk?

Response:

OHRP referenced in the articles cited in a letter dated June 4, 2013, from OHRP to the University of Alabama the specific scientific data that existed at the start of the SUPPORT study that OHRP relied on in reaching its conclusion. The letter and article references can be found on OHRP's web site at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf). NIH subsequently responded in disagreement with the conclusions and stated the more recent data generated with more sophisticated oxygen-monitoring and oxygen-measurement devices showed no increased risk of death or neurological damage (see http://www.nejm.org/doi/full/10.1056/NEJMp1306986). OHRP and NIH are continuing to review these considerations. In addition, HHS will hold a public meeting to seek public input and comment on how certain provisions of the HHS requirements related to the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the nonresearch context on August 28, 2013.

2. If no such data existed, could you please explain why it would be scientifically credible or ethical to explain unknown risks of a study?

Response:

Please see response above regarding specific scientific data. HHS does not and has not questioned whether the design of the SUPPPORT study was ethical.

3. What is the process for appealing the findings of OHRP? Is there a mechanism for having an independent review of OHRP actions especially when they are so universally called into question as in this case? (Please see, for example, editorials and correspondence in the New England Journal of Medicine and The Hastings Center Bioethics Forum).

Response:

OHRP's compliance oversight procedures state that an institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation, http://www.hhs.gov/ohrp/compliance/evaluation/index.html. OHRP has no recollection of any such requests for reconsideration from an institution against which OHRP made a determination of noncompliance. Historically, OHRP has received such requests only from complainants concerned that OHRP did not agree with their allegations of noncompliance. If such complainants are unsatisfied with

the response of the OHRP Director, OHRP informs them that they may communicate with the Principal Deputy Assistant Secretary for Health and the Assistant Secretary for Health and ask them to review the matter.

Bartok, Lauren (NIH/OD) [C]

From: Cochran, Norris (HHS/ASFR)
Sent: Tuesday, July 23, 2013 9:44 AM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH)
Cc: Lewis, Caya (HHS/IOS); Devaney, Stephanie (NIH/OD) [E]
Subject: Final QFR
Attachments: SUPPORT Clinical Trial.docx

Thank you again, all. We will send the attached final to the Committee now.

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 8:39 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Cochran, Norris (HHS/ASFR)
Cc: Lewis, Caya (HHS/IOS); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Given that our primary issue was not the age of data cited by ohrp but the relevance of more recent data, please use this edit.

(b)(5)

-----Original Message-----
From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, July 22, 2013 7:42 PM
To: Hudson, Kathy (NIH/OD) [E]; Cochran, Norris (HHS/ASFR)
Cc: Lewis, Caya (HHS/IOS); Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Final QFR

Consider Kathy's comments, but again, can live w/this. Thanks, all.

Wanda K Jones, DrPH
Principal Deputy Assistant Secretary for Health US Department of Health and Human Services
200 Independence Ave SW
Washington, DC 20201

Sent from my Blackberry while I'm away from my desktop.

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 06:01 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Jones, Wanda K. (DHHS/OS/OASH); Lewis, Caya (HHS/IOS); Devaney, Stephanie (NIH/OD) [E]
Subject: Re: Final QFR

Well, (b)(5) but we can live with this if you don't like my suggested sentence.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH

301 496 1455
kathy.hudson@nih.gov

On Jul 22, 2013, at 5:56 PM, "Cochran, Norris (HHS/ASFR)" <Norris.Cochran@HHS.GOV> wrote:

> Thanks, Kathy. (b)(5) Wanda, does the below work?
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(b)(5)

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> Cc: Devaney, Stephanie (NIH/OD) [E]
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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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(b)(5)

>
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> SUPPORT Clinical Trial
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(b)(5)

(b)(5)

[redacted]

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> Attached please find:
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> 1. The OHRP letter to UAB sent june 4.
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> 2. The New England Journal of Medicine Article that was extensively reviewed and cleared by HHS.
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> In this article we say, " The federal Office for Human Research Protections (OHRP), which is charged with providing leadership in the protection of the rights, welfare, and well-being of persons involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS), asserted in March 2013, on the basis of its own examination of the evidence, that the SUPPORT researchers failed to provide prospective parents sufficient information about the risks posed by the study. After a detailed review of the protocol, the relevant consent documents, and the research literature, we respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPORT study commenced."
> 3. The Federal Register Notice announcing meeting to get input on this issue. This notice is from the Office of the Secretary and says, “Through the public reaction to OHRP’s determination letter, HHS has become aware of differing perspectives in the scientific, research, and ethics communities about these issues and how the relevant requirements of the HHS protection of human subjects regulations should apply to research studying standard of care interventions.”
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(b)(5)

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(b)(5)

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(b)(5)

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> From: Jones, Wanda K. (DHHS/OS/OASH)
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> If you have any questions, don't hesitate to reach out to me.   Wanda
>
>
> Wanda K. Jones, Dr.P.H.
> Principal Deputy Assistant Secretary for Health US Department of
> Health and Human Services
> 200 Independence Ave. SW, Room 716G
> Washington, DC 20201
> Phone 202 260 4432
> Main 202 690 7694
> Fax 202 690 6960

> Email wanda.jones@hhs.gov<mailto:wanda.jones@hhs.gov>
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> "Mobilizing leadership in science and prevention for a healthier nation"
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>
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Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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Butler, Brenda (NIH/OD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, July 22, 2013 8:37 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: Final QFR

No, the problem is that the so-called data that ohrp is referring to is down in very very low oxygen levels and thus irrelevant. All the other so-called data they refer to is not data at all but concerns and questions. I am worried I might get hit by an asteroid tomorrow on my way to work but that is not data.

How about this? I will send to the group as well.

(b)(5)

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 6:26 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Re: Final QFR

Kathy (b)(5)
(b)(5)

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Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

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> SUPPORT Clinical Trial
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> The University of Alabama at Birmingham (UAB) recently received a letter from the Office for Human Research Protections (OHRP) about the SUPPORT clinical trial, a research study of premature infants and supplemental oxygen. In the letter, OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study.
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(b)(5)

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> Wanda K. Jones, Dr.P.H.
> Principal Deputy Assistant Secretary for Health US Department of
> Health and Human Services
> 200 Independence Ave. SW, Room 716G
> Washington, DC 20201
> Phone 202 260 4432
> Main 202 690 7694
> Fax 202 690 6960
> Email wanda.jones@hhs.gov<mailto:wanda.jones@hhs.gov>
>
> "Mobilizing leadership in science and prevention for a healthier nation"
>

Bartok, Lauren (NIH/OD) [C]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Monday, July 22, 2013 5:51 PM
To: Boskent, Celeste (NIH/OD) [E]
Cc: Marshall, Lisa (NIH/OD) [E]; Brewer, Ann (NIH/OD) [E]; Schulke, Hilda (NIH/OD) [E]; McManus, Ayanna (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]
Subject: July 23 - Mtg with OS staff and Dr. Hudson re: Next Steps on SUPPORT
Attachments: FRN 2013-15160.pdf; Draft Precis-for exercising OHRP guidance-6-18.docx; HHS Meeting - Next Steps on SUPPORT - doc for KH andFC 7-22-13.docx

Hi Celeste –

Attached here for the meeting folders are the documents that I just sent to Kathy and Francis for the meeting on SUPPORT tomorrow 7/23 at 3:00p.

Best,
Steph

Stephanie Devaney, Ph.D.
Science Policy Analyst
Special Assistant to the Deputy Director for Science, Outreach, and Policy
Office of the Director
National Institutes of Health
1 Center Drive, Building 1/103
Bethesda, MD 20892
Phone: 301-402-1994
stephanie.devaney@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

responsibilities regarding the maintenance and availability of inventory records of assets. Without this information or ability to access the information, after an ownership change, the Government would be unable to ascertain whether contractor assets were properly valuated. The cost principles at FAR 31.205–52 address the allowability of certain costs resulting from asset valuations following business combinations. In order to administer the cost principles adequately, the information required by FAR 52.215–19 is necessary.

Comment: The respondent commented that the agency did not accurately estimate the public burden challenging that the agency's methodology for calculating it is insufficient and inadequate and does not reflect the total burden.

Response: Serious consideration is given, during the open comment period, to all comments received and adjustments are made to the paperwork burden estimate based on reasonable considerations provided by the public. This is evidenced, as the respondent notes, in FAR Case 2007–006 where an adjustment was made from the total preparation hours from three to 60. This change was made considering particularly the hours that would be required for review within the company, prior to release to the Government.

The burden is prepared taking into consideration the necessary criteria in OMB guidance for estimating the paperwork burden put on the entity submitting the information. For example, consideration is given to an entity reviewing instructions; using technology to collect, process, and disclose information; adjusting existing practices to comply with requirements; searching data sources; completing and reviewing the response; and transmitting or disclosing information. The estimated burden hours for a collection are based on an average between the hours that a simple disclosure by a very small business might require and the much higher numbers that might be required for a very complex disclosure by a major corporation. Also, the estimated burden hours should only include projected hours for those actions which a company would not undertake in the normal course of business.

Upon consideration of the respondent's comments and review of Fiscal Year 2012 (FY12) Federal Procurement Data System (FPDS) information an adjustment is being made to the estimated annual burden. Based on FPDS information approximately 1200 novations and non-novated mergers and acquisitions were recorded in FY12 as descriptions for modifications. However, it is estimated that 50 percent or 600 of such actions will require the contractor to meet the requirements specified at FAR 52.215–19. The clause is only required to be inserted in solicitations and contracts for which it is contemplated that certified cost or pricing data will be required or for which any pre-award or post-award cost determination will be subject to *Subpart 31.2*. The estimate of hours per response is adjusted upwards to partly allow for the internal coordination and analysis before submitting the information to the Government as stated by the respondent. However the significant adjustment suggested was not made because, apart from a notification to the ACO, the requirements of the clause are passive, requiring contractors to maintain rather than to create records to meet the specific requirements for Government submission, and should be part of the normal course of doing business. At any point, members of the public may submit comments for further consideration, and are encouraged to provide data to support their request for an adjustment.

C. Annual Reporting Burden

Respondents: 600.

Responses per Respondent: 1.

Total Responses: 600.

Hours per Response: 5.

Total Burden Hours: 3000.

Obtaining Copies of Proposals: Requesters may obtain a copy of the information collection documents from the General Services Administration, Regulatory Secretariat (MVCB), 1275 First Street NE., Washington, DC 20417, telephone (202) 501–4755. Please cite OMB Control No. 9000–0115, Notification of Ownership Changes, in all correspondence.

Dated: June 21, 2013.

William Clark,

Acting Director, Office of Governmentwide Acquisition Policy, Office of Acquisition Policy, Office of Governmentwide Policy.

[FR Doc. 2013–15300 Filed 6–25–13; 8:45 am]

BILLING CODE 6820–EP–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Notice of a Department of Health and Human Services Public Meeting and Request for Comments on Matters Related to the Protection of Human Subjects and Research Studying Standard of Care Interventions

AGENCY: Office of the Secretary, Department of Health and Human Services.

ACTION: Notice of meeting and request for comments.

SUMMARY: The Department of Health and Human Services (HHS) is announcing a public meeting to seek public input and comment on how certain provisions of the HHS requirements related to the protection of human subjects should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically is requesting input regarding how an institutional review board (IRB) should assess the risks of research involving randomization to one or more treatments within the standard of care for particular interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. HHS is seeking participation in the meeting and written comments from all interested parties, including, but not limited to, IRB members, IRB staff, institutional officials, research institutions, investigators, research subject advocacy groups, ethicists, and the regulated community at large. This meeting and the written comments are intended to assist HHS, through the Office for Human Research Protections (OHRP), Office of the Assistant Secretary for Health (OASH), in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects. HHS is seeking input on a number of specific questions but is interested in any other pertinent information participants in the public meeting would like to share.

DATES: *Meeting:* The public meeting will be held on August 28, 2013, from 9 a.m. to 5 p.m.

Deadline for Registration for Participants (not Presenting) at the Public Meeting and Submitting Requests for Special Accommodations: Registration to attend the public meeting and requests for special accommodations must be received no later than 5 p.m. on August 14, 2013.

Deadline for Registration of Presenters at the Public Meeting: Registration to present at the public meeting must be received no later than 5 p.m. on August 7, 2013.

Deadline for Submission of Written Comments for the Public Meeting: Written comments for discussion at the public meeting must be received no later than 5 p.m. on August 7, 2013. In addition to materials submitted for discussion at the public meeting, individuals may submit other written comments after the public meeting, as specified in the **ADDRESSES** section of this notice. These comments must be received no later than 5 p.m. on September 9, 2013, for consideration by HHS.

ADDRESSES: The Public Meeting will be held at the Department of Health and Human Services, Hubert H. Humphrey Building, 200 Independence Ave. SW., Great Hall, Washington, DC 20201; Metro: Federal Center SW station.

In addition, we are providing an alternative to attending the meeting in person; participants may view the public meeting via live streaming technology. Information on that option is provided in section II.D. of this notice.

Registration and Special Accommodations: While there is no registration fee, individuals planning to attend the public meeting in person must register to attend. Registration may be completed by sending an email to *OHRP@hhs.gov*, with the subject line "Registration for HHS Public Meeting"; or a request to register may be sent to: Registration for HHS Public Meeting, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852. Please include your name, address, telephone number, email address, and fax number. If you would like to present at the public meeting, please state this in the registration submission.

Registration to attend the public meeting will be accepted on a first-come, first-served basis. If seating capacity has been reached, you will be notified that the meeting has reached capacity.

Registration to present at the public meeting will be accepted on a first-come, first-served basis. HHS has included questions for comment in section III of this document. Please identify by number each question you wish to address in your presentation and the approximate time requested. HHS will do its best to accommodate requests to speak. HHS will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin. Once HHS notifies registered presenters of their scheduled times, presenters should submit a copy of each presentation, identified with docket number HHS–OPHS–2013–0004, to *http://www.regulations.gov.*

Individuals who need special accommodations should contact staff listed in the **FOR FURTHER INFORMATION CONTACT** section of this notice.

Submission of Comments for the Public Meeting

Submit electronic comments, identified with docket number HHS–OPHS–2013–0004, to *http://www.regulations.gov.*

Submit written comments to Comments for HHS Public Meeting, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dr. Jerry Menikoff, Director, Office for Human Research Protections, Department of Health and Human Services, 1101 Wootton Parkway, Suite 200, Rockville, MD 20852; phone 240–453–6900; email *Jerry.Menikoff@hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

A. HHS Protection of Human Subjects Regulations

HHS, through OHRP, regulates research involving human subjects conducted or supported by HHS in regulations. The HHS human subjects protection requirements pertain to several different entities, including the IRB charged with reviewing non-exempt human subjects research.

The IRB is an administrative body that takes the form of a board, committee, or group, and is responsible for conducting the initial and continuing review of research involving human subjects. The IRB must have authority to approve, require modification in (in order to secure approval), or disapprove all research activities regulated by HHS. An IRB's primary purpose in reviewing research is to ensure the protection of the rights and welfare of human research subjects. In order to approve research, an IRB is required to make certain determinations, including that the following criterion is met:

> Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. 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). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

The HHS human subjects protections further require that, unless this requirement is waived by the IRB, an investigator must obtain informed consent from research subjects prior to the subjects' participation in the research, and that, in this informed consent process, the subjects must be provided "a description of any reasonably foreseeable risks or discomforts to the subject."

B. OHRP's Compliance Oversight Investigation of SUPPORT

On March 7, 2013, OHRP issued a compliance oversight determination letter regarding its investigation into "The Surfactant, Positive Pressure, and Oxygenation Randomized Trial" (SUPPORT) clinical trial (*http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf*), in which OHRP determined that certain risks related to the interventions being studied in the SUPPORT trial were required by the HHS protection of human subjects regulations to be disclosed to the research subjects, and the subjects were not informed of these risks. OHRP's view of the SUPPORT trial, as described in this determination letter, triggered extensive public discussions regarding (1) what risks to subjects are presented by clinical trials studying interventions that are standard of care in the clinical treatment context, such that an IRB must evaluate those risks in relation to the anticipated benefits of the research; and (2) how an IRB should assess whether those risks are reasonably foreseeable such that the risks must be described to subjects in informed consent. Through the public reaction to OHRP's determination letter, HHS has become aware of differing perspectives in the scientific, research, and ethics communities about these issues and how the relevant requirements of the HHS protection of human subjects regulations should apply to research studying standard of care interventions.

II. Public Meeting

A. Purpose and Scope of the Meeting

The public meeting is intended to provide an opportunity for broad public participation and comment concerning how the HHS human subjects

protections requirements should be applied to research studying one or more interventions which are used as standard of care treatment in the non-research context. HHS specifically is requesting input regarding how an IRB should assess the risks of research involving randomization to one of more standard of care interventions, and what reasonably foreseeable risks of the research should be disclosed to research subjects in the informed consent process. This meeting and the written comments are intended to assist HHS, through the OHRP, OASH, in developing guidance regarding what constitutes reasonably foreseeable risk in research involving standard of care interventions such that the risk is required to be disclosed to research subjects.

While HHS is considering whether other processes should be incorporated into OHRP's compliance oversight procedures and guidance, including, but not limited to, consultation with subject matter experts during the course of a compliance oversight investigation, and an administrative process for appealing OHRP determinations of noncompliance, this meeting is not intended to specifically address possible revisions to OHRP's compliance oversight procedures.

B. Format of the Meeting

The meeting will be conducted by a panel of HHS officials, including the Director of OHRP. The majority of the meeting will be reserved for presentations of comments, recommendations, and data from registered presenters. The time for each presenter's comments will be determined by HHS and will be based on the number of registered presenters. Presenters will be scheduled to speak in the order in which they register. Only the HHS panel members may question any presenter during or at the conclusion of each presentation. The meeting will be recorded and transcribed.

In addition, written comments will also be accepted and presented at the meeting, time permitting, if they are received by the date specified in the **DATES** section of this notice.

C. Security and Building Guidelines

Because the public meeting will be located on federal property, for security reasons any persons wishing to attend this meeting must register by the date specified in the **DATES** section of this notice. Attendees should allow sufficient time to go through the security checkpoints. Attendees should arrive at the Hubert H. Humphrey Building no later than 8:30 a.m.

Security measures include the following:

- Presentation of government-issued photographic identification to the Federal Guard Service personnel.
- Passing through a metal detector and inspection of items brought into the building; note that all items brought to HHS are subject to inspection.

Note: Individuals who are not registered in advance will not be permitted to enter the building and will be unable to attend the meeting in person. The public may not enter the building earlier than 45 minutes prior to the convening of the meeting(s). All visitors must be escorted while in the building.

D. Live Streaming Information

For participants who cannot attend the public meeting in person there will be an option to view the public meeting via live streaming technology. Information on the option to view the meeting via live streaming technology will be posted at a later time on the OHRP Web site at *http://www.hhs.gov/ohrp*. Any other updates to information on the meeting will be posted on the OHRP Web site.

III. Issues for Discussion

HHS invites comment at the public meeting about how an IRB should assess the risks of research involving randomization to one or more standard of care interventions, and what risks of the research should be disclosed to research subjects in the informed consent process. HHS is specifically interested in public input on the following questions:

1. How should an IRB assess the risks of standard of care interventions provided to subjects in the research context?

a. Under what circumstances should an IRB consider those to be risks that may result from the research?

b. Under what circumstances should an IRB refrain from considering those risks as unrelated to the research?

c. What type of evidence should an IRB evaluate in identifying these risks?

2. What factors should an IRB consider in determining that the research-related risks of standard of care interventions, provided to research subjects in the research context, are reasonably foreseeable and therefore required to be disclosed to subjects?

a. What criteria should be used by the IRB to evaluate whether the risks to subjects are reasonably foreseeable?

3. How should randomization be considered in research studying one or more interventions within the standards of care? Should the randomization procedure itself be considered to present a risk to the subjects? Why or why not? If so, is the risk presented by randomization more than minimal risk? Should an IRB be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions? Why or why not?

4. How, and to what extent, does uncertainty about risk within the standard of care affect the answers to these questions? What if the risk significantly varies within the standard of care?

5. Under what circumstances do potential risks qualify as reasonably foreseeable risks? For example, is it sufficient that there be a documented belief in the medical community that a particular intervention within the standard of care increases the risk of harm, or is it necessary that there be published studies identifying the risk?

IV. Transcripts

As soon as a transcript of the public meeting is available, it will be accessible on the OHRP Web site, *http://www.hhs.gov/ohrp*. A transcript also will be available in either hardcopy or on CD–ROM, after submission of a Freedom of Information request. Written requests are to be sent to the PHS FOIA Office, 7700 Wisconsin Avenue, Suite #920, Bethesda, MD 20857; telephone (301) 492–4800; fax (301) 492–4848; email *FOIARequest@psc.hhs.gov*.

Dated: June 19, 2013.

Howard K. Koh,

Assistant Secretary for Health.

[FR Doc. 2013–15160 Filed 6–25–13; 8:45 am]

BILLING CODE 4150–36–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Meeting of the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health

AGENCY: Office of the Surgeon General of the United States Public Health Service, Office of the Assistant Secretary for Health, Office of the Secretary, Department of Health and Human Services.

ACTION: Notice.

SUMMARY: In accordance with Section 10(a) of the Federal Advisory Committee Act, Public Law 92–463, as amended (5 U.S.C. App.), notice is hereby given that a meeting is scheduled to be held for the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health (the "Advisory Group"). The meeting will be open to the public.

Workshop on Informed Consent for Standard of Care Research

(b)(5)

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Bartok, Lauren (NIH/OD) [C]

From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 5:50 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Final QFR

Follow Up Flag: Follow up
Flag Status: Completed

Kathy - what do you think?

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, July 22, 2013 05:41 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Cochran, Norris (HHS/ASFR); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

Yes, on the OHRP side, we can live with this.

Jerry

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, July 22, 2013 4:53 PM
To: Cochran, Norris (HHS/ASFR); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

I'm satisfied with this, Norris, if Caya, Jerry and Kathy can live with it. Thank you for bringing your expertise to bear here, a positive presentation for HHS. Wanda

PS Norris--Are you signed up for the diplomatic corps?

From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 4:50 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

Thank you, Wanda. Would the below work for all?

(b)(5)

(b)(5)

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, July 22, 2013 3:42 PM
To: Cochran, Norris (HHS/ASFR); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

Do not want to convey the public meeting is about SUPPORT, right? Instead, the broader issue of conducting research on standard of care treatments? Can't avoid SUPPORT, and certainly the impetus, but I'd probably split that last sentence to say that HHS will hold a public meeting.

From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 3:39 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

(b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 2:56 PM
To: Cochran, Norris (HHS/ASFR); Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

Norris,

Attached please find:

1. The OHRP letter to UAB sent june 4.

2. The New England Journal of Medicine Article that was extensively reviewed and cleared by HHS.

In this article we say, " The federal Office for Human Research Protections (OHRP), which is charged with providing leadership in the protection of the rights, welfare, and well-being of persons involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS), asserted in March 2013, on the basis of its own examination of the evidence, that the SUPPORT researchers failed to provide prospective parents sufficient information about the risks posed by the study. After a detailed review of the protocol, the relevant consent documents, and the research literature, we respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPORT study commenced."
3. The Federal Register Notice announcing meeting to get input on this issue. This notice is from the Office of the Secretary and says, "Through the public reaction to OHRP's determination letter, HHS has become aware of differing perspectives in the scientific, research, and ethics communities about these issues and how the relevant requirements of the HHS protection of human subjects regulations should apply to research studying standard of care interventions."

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Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: Re: Final QFR

Thank you, Kathy. If you have them handy, please send me her public statements

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 02:04 PM
To: Cochran, Norris (HHS/ASFR); Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

I will of course defer to ASFR on what direction to take (b)(5)

(b)(5)

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 12:58 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Thanks, Kathy and Wanda. (b)(5)

(b)(5)

(b)(5)

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 12:46 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

I sent you a wrong version of our edits.

Can you take a look at this version please?

Sorry I had attachment problems.

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, July 21, 2013 12:37 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Wanda, Howard, Jerry,

Thanks for taking another stab at the Shelby QFR response. (b)(5)

(b)(5)

Please let me know what you think of this proposed revision.

Thanks
Kathy

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Friday, July 19, 2013 4:28 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Fw: Final QFR

Kathy - Please see below and attached. Please let me know of any major issues as soon as you can. Thank you.

Norris

----- Original Message -----
From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Friday, July 19, 2013 04:21 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Grifka, Michelle (HHS/OASH); Gannon, Jennifer (HHS/ASFR)
Subject: Final QFR

Norris, We have taken language exactly from the (second) letter sent to UAB, except that we've added a regulatory citation that was implicit in the letter's reference to what 'society requires'; in this particular context, that might not be so obvious.

If you have any questions, don't hesitate to reach out to me. Wanda

Wanda K. Jones, Dr.P.H.
Principal Deputy Assistant Secretary for Health US Department of Health and Human Services
200 Independence Ave. SW, Room 716G
Washington, DC 20201
Phone 202 260 4432
Main 202 690 7694
Fax 202 690 6960
Email wanda.jones@hhs.gov

"Mobilizing leadership in science and prevention for a healthier nation"

Bartok, Lauren (NIH/OD) [C]

From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 3:12 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
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Wanda K. Jones, Dr.P.H.
Principal Deputy Assistant Secretary for Health US Department of Health and Human Services
200 Independence Ave. SW, Room 716G
Washington, DC 20201
Phone 202 260 4432
Main 202 690 7694
Fax 202 690 6960
Email wanda.jones@hhs.gov

"Mobilizing leadership in science and prevention for a healthier nation"

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-6900
FAX: 240-453-6909

June 4, 2013

Richard B. Marchase, Ph.D.
V.P. for Research & Economic Development
University of Alabama at Birmingham
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

Research Project:	The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
Principal Investigator:	Dr. Waldemar A. Carlo
HHS Protocol Number:	2U10HD034216

Dear Dr. Marchase:

In the wake of extensive scientific and public discussions since our March 7, 2013, determination letter in the SUPPORT study, OHRP has become aware of widespread misunderstanding about the risks that are required to be disclosed in obtaining informed consent for certain types of clinical trials. Our goal in this letter is to clarify several issues related to our determination.

At the outset, we wish to emphasize that OHRP does not and has never questioned whether the design of the SUPPORT study was ethical. It was a study that asked important questions and produced information that promises to advance both scientific knowledge and clinical care. Rather, consistent with OHRP's mission to protect human subjects of research, the overarching concern of our determination was the adequacy of informed consent, a bedrock principle of research involving human subjects.

To make truly informed decisions about whether or not to participate in a research study, potential volunteers or their parents or guardians are entitled to certain information, including a description of reasonably foreseeable risks. We acknowledge that the UAB consent form included language that reflected then-current research suggesting that lower saturation targets reduced the risk of retinopathy of prematurity (ROP), as well as language about the potential risks of ROP with prolonged use of supplemental oxygen. However, the "Risks" section of that form failed to mention and appropriately describe, as it should have, that relationship. More

significantly, neither the "Risks" section nor any other portion of the form mentioned any risks associated with lower oxygen levels.

OHRP recognizes that the SUPPORT investigators did not design the study with the expectation that they would find a difference in mortality rates between the high and low oxygen groups. Whereas much earlier studies of oxygen supplementation in premature babies had shown risks of mortality and neurological damage at very low oxygen levels, more recent studies did not demonstrate such risks. Consequently, when the SUPPORT study was initiated, there was no clear recent evidence indicating that different oxygenation levels within the then-current standard of care (85%-95%) would produce differences in neurological damage or survival.

However, the medical profession looks at many factors when assessing potential risks. At the outset of the SUPPORT study, many in the research and clinical communities remained concerned about the possible relationship between low oxygen and increased mortality and neurodevelopmental problems within the oxygen ranges that were to be evaluated in that study.[1] Indeed, such concerns were a core reason why the study was conducted. Those concerns were sufficient to affect clinical decisions and discouraged some doctors from treating premature infants at lower oxygen levels.

Indeed, descriptions of the process of designing the SUPPORT study and four similar studies conducted in other countries indicate a clear awareness of such concerns and the need to resolve them. This is evidenced by multiple statements from the SUPPORT investigators and other experts,[2] who identified the important need for a large randomized study with sufficient power to detect differences in mortality rates of 5% or greater.

---

[1] See note 2, below.

[2] "In 2003, an eminent international group of over 30 trialists, bio-statisticians, neonatologists, ophthalmologists and developmental paediatricians was convened to conduct [what would become known as] the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration." Askie et al., BMC Pediatrics 2011 11:6, at page 3. That collaboration eventually included the SUPPORT study and four similar studies conducted within Canada (COT), the United Kingdom (BOOST-II UK), Australia (BOOST-II), and New Zealand (BOOST NZ). The initial thinking behind this group of studies was "outlined in a [2003] commentary in *Pediatrics*" in which Cole et al., Resolving Our Uncertainty About Oxygen Therapy, *Pediatrics* 2003;112:1415, discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." They also noted a particular challenge in recruiting neonatal units to participate: some units "regard [oxygen levels greater than 90%] as mandatory," and might therefore be unwilling to participate in a study in which one-half of the infants would be randomized to levels below 90%. To recruit such units, they suggested using "cohort data suggesting that lower levels of saturation can reduce retinopathy without increasing mortality or cerebral palsy."

Subsequent official statements regarding SUPPORT and the other four trials, issued prior to the 2010 results from SUPPORT, demonstrate that resolving those "real concerns" about mortality risks at the low oxygen end remained a major issue for these studies. On the official registration system for clinical trials in the U.S., clinicaltrials.gov, the SUPPORT researchers, in 2005, provided a one-sentence description, saying that it "will determine whether or not [the] two management strategies affect chronic lung disease and survival of premature infants." http://clinicaltrials.gov/archive/NCT00233324/2005_10_04 The description provided on that same database for the

Some commentators, in discussing the risks involved in the SUPPORT study, have attached great importance to the fact that all the oxygen levels to which the infants were assigned were within the range of the standard care.[3] But they draw inappropriate conclusions from that fact. Medicine is an imperfect science. When considerable uncertainty exists about the best way to treat a particular medical problem, the range of what can be considered standard care often is quite broad, to allow physicians to exercise clinical judgment on behalf of their patients.[4] Indeed, a core principle of medical ethics requires physicians to make such judgments, even in the face of uncertainty. All of us, as patients, rely on our doctors to do precisely that.

This principle has direct bearing on the SUPPORT study. When there is a range of oxygen levels within the standard of care, clinicians (and their institutions) often do, in fact, make their own determinations regarding which oxygen levels within that range to employ in treating their patients. Some physicians, recognizing the particular concerns about risks near the low (85%) and high (95%) ends of that range, might choose to avoid one or both of those regions.

The version of the consent form used at one SUPPORT site specifically acknowledged this to be the case; at that center, for clinical purposes, oxygen saturation was "kept between 88 and 94%."[5] Assuming the researchers achieved the distribution of oxygen levels they were trying to attain, research subjects at that site had a greater than 25% chance of being treated with an oxygen saturation between 85 and 88%, whereas, for those treated outside the study, the likelihood of being treated with oxygen in that range was quite small. Thus, by participating in

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Canadian trial in 2008 states that a randomized trial "is urgently needed and long overdue to determine whether oxygen exposure can be reduced safely in extremely preterm infants without increasing the risk of hypoxic death or disability." The United Kingdom protocol noted that "restricting oxygen exposure to minimize [the possibility of severe retinopathy] risks increasing early mortality." http://clinicaltrials.gov/archive/NCT00637169/2008_03_14 See also Silverman WA: A cautionary tale about supplemental oxygen: the albatross of neonatal medicine. *Pediatrics* 2004 (113):394-396 ("For decades, the optimum range of oxygenation (to balance four competing risks: mortality, ROP blindness, chronic lung disease, and brain damage) was, and remains to this day, unknown"); Tin et al, Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106–F110 ("Because mortality went undocumented in the first of the large trials of oxygen administration, we do not even know if there is a price to be paid for controlling administration strictly enough to minimise the risk of severe retinopathy.") . A Cochrane Collaboration review in 2009 specifically looked at the relationship between oxygen levels and mortality, concluding that the correct range to use was still not yet known. With regard to the most recent studies (from 2001 to 2004) showing no increased mortality at lower oxygen ranges, it noted: "these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide," and that the SUPPORT and other four studies were collecting data to "help resolve this remaining question." Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review). Cochrane Database of Systematic Reviews 2009(1).

[3] Drazen JM, Solomon CG, Greene MF. Informed Consent and SUPPORT. N Engl J Med 2013;368:1929; Magnus D, Caplan AL. Risk, Consent and SUPPORT. N Engl J Med 2013;368:1864; Lantos JD. OHRP and Public Citizen are Wrong about Neonatal Research on Oxygen Therapy. Hastings Center Bioethics Forum, April 18, 2013;.

[4] Shepherd L. The SUPPORT Study and the Standard of Care. Hastings Center Bioethics Forum, May 17, 2013.

[5] SUPPORT consent form, Tufts Medical Center, available at http://www.citizen.org/documents/support-study-consent-form.pdf.

the study, the treatment of such subjects was substantially altered to make it much more likely that they would be within the range in which there were significant concerns about increased mortality.

And this circumstance is likely not unique to that site. As another of the consent forms noted, the "aim in many units is to keep oxygen saturations between 88 and 92%."[6] For institutions with those clinical care policies, participating in the study would have significantly increased the chance of an infant being assigned to oxygen levels at both the very low (85 to 88%) and the very high ends (92 to 95%), as opposed to the level they would have received, had they not been in the study.[7]

Unless, as is extraordinarily unlikely, an institution used for clinical purposes exactly the same randomization assignment procedure that was used in the SUPPORT trial, every child in the SUPPORT trial experienced some change in the likelihood of being assigned to the various oxygen levels. And as the above discussion demonstrates, for at least some of the children participating in the SUPPORT trial, the effect of such participation was to specifically increase their likelihood of being assigned to oxygen levels close to either end of the range of standard care – and thus to oxygen levels at which, as a clinical matter, they would not have been assigned by their individual physicians, had they not been in the study.

Ultimately, the issues in this case come down to a fundamental difference between the obligations of clinicians and those of researchers. Doctors are required, even in the face of uncertainty, to do what they view as being best for their individual patients. Researchers do not have the same obligation: Our society relaxes that requirement because of the need to conduct research, the results of which are important to us all. As a modest but crucial trade-off in allowing researchers such flexibility, society requires that researchers tell subjects how participating in the study might alter the risks to which they are exposed. For some if not many of the subjects in the SUPPORT study, research participation increased the chance that they were treated at one or another end of the standard of care range. Given the requirement that subjects be apprised of "reasonably foreseeable risks," it would seem appropriate that the parents of the infants should have been informed of the real concerns within the medical community regarding those oxygen levels.[8]

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[6] SUPPORT consent form, Duke University Health System, available at http://www.citizen.org/documents/support-study-consent-form.pdf .

[7] Imagine, for example, an institution whose clinical standard allowed the full range of standard care to be used, with the pulse oximeter alarm set to go off at the levels of 85% and 95%, and with the goal of trying to keep the infant in the middle of that range (near 90%). Even under that scenario, by participating in the trial, the likelihood of the infant ending up in the more extreme values (85 to 87% or 93 to 95%) would, under some plausible assumptions, have nearly doubled.

[8] As noted above, the UAB consent form mentioned no risks with regard to the use of lower oxygen levels. In contrast, a 2005 version of the consent form used in the New Zealand BOOST study included this language: "Too low oxygen in the blood for long periods may 1) increase the risk the baby will not survive or contribute to poor growth; 2) raise blood pressure in the lungs and contribute to bronchopulmonary dysplasia; 3) damage the brain cells and lead to developmental problems. . . . . The aim of this study is to determine, *within the range of oxygen saturation values currently used in the treatment of preterm babies (85-95%)*, whether targeting the lower end of

OHRP recognizes that applying the "reasonably foreseeable risk" concept to randomized studies of standard of care treatments is a complex undertaking. We want to be clear, however, that it is not necessary to disclose all theoretical risks present at the outset of every study. Moreover, disclosure of a risk is unnecessary when study participation has no potential to increase or modify that risk compared to what would have happened had the subject not been in the study.

The facts regarding the SUPPORT study and what was known about the use of oxygen to treat premature infants also are complicated. Accordingly, we appreciate that there is justification for an incomplete understanding of how those rules might apply to this study. In addition, there are some who disagree with OHRP's analysis of how the regulations should apply to such studies. Indeed, some of the researchers involved in the SUPPORT study and others have argued that there was no need for researchers to have obtained any consent from parents before placing their children in this study.[9] This discussion takes place in the midst of a much broader discussion regarding a proposal from a distinguished group of scholars that is receiving prominent attention, which argues for completely eliminating the need for any consent in similar studies – a change that would involve a major reframing of the rules for protecting research subjects.[10]

These are crucially important issues, not just with regard to our ability to be able to conduct research with appropriate oversight, but also with regard to fundamental questions about the obligations owed by doctors to patients. Given their importance, we recognize OHRP's obligation to provide clear guidance on what the rules are with regard to disclosure of risks in randomized studies whose treatments fall within the range of standard of care. We are committed to doing that, and doing it promptly. Most important, given the controversy engendered by our determination in the SUPPORT study, we will ensure that the process for producing such guidance is as open as possible, to allow input from all interested parties. Thus, not only will we engage in the usual notice and comment process with regard to draft guidance, we will also conduct an open public meeting on this topic.

In addition, in further recognition of the concerns noted above, we have put on hold all compliance actions against UAB relating to the SUPPORT case, and plan to take no further

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this range (85-89%) compared to upper end of this range (91-95%), beginning within 24 hours of birth, is safe and effective in reducing serious vision (ROP) and lung (BPD) problems without increasing mortality or neurodevelopmental disability." (BOOST-NZ consent form, July 2005, personal communication from Brian Darlow, principal investigator of BOOST-NZ) Had such language been in the UAB consent form, there would likely have been no OHRP finding with regard to non-disclosure of the risks relating to mortality and neurodevelopmental problems. And the NeOProM 2011 write-up, mentioned in note 2 above, using only pre-2005 references, describes the risks issue as follows: "There are two opposing concerns. Less inspired oxygen [under 90%] may increase patent ductus arteriosus, pulmonary vascular resistance and apnoea, and impair survival and neuro-development. More inspired oxygen [greater than 90%] may increase severe [retinopathy] and chronic lung disease."

[9] Rich W et al. Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative. Pediatrics 2012;129:480; Whitney SN. The Python's Embrace: Clinical Research Regulation by Institutional Review Boards. Pediatrics 2012;129:576.

[10] Faden RR et al. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. Hastings Center Report Special Report 2013;43(1):S16.

action in studies involving similar designs until the process of producing appropriate guidance is completed.

OHRP's top priority remains that of protecting research participants. For this reason, we look forward to the forthcoming public discussion, and assuring that important research can proceed both with appropriate protection of subjects and without confusion about which risks must be disclosed.

We appreciate the continued commitment of your institutions to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:
Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI
Mr. David Borasky, Chair IRB#1, RTI
Ms. Angela Greene, Chair IRB#2, RTI
Dr. Juesta M. Caddell, Chair IRB#3, RTI
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Alan E. Guttmacher, Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
Dr. Yvonne Maddox, Deputy Director, NICHD
Dr. Rosemary Higgins, Program Scientist, NICHD
Dr. Robert H. Miller, Case Western Reserve University
Dr. Nancy C. Andrews, Duke University
Dr. Janice D. Wagner, Wake Forest University School of Medicine
Mr. Thomas Hughes, Women and Infants Hospital of Rhode Island
Dr. Clyde L. Briant, Brown University
Dr. Thomas N. Parks, University of Utah, School of Medicine
Dr. Jane Strasser, University of Cincinnati
Ms. Susan Blanchard, BBA, Tufts Medical Center
Ms. Angela Wishon, University of Texas Southwestern Medical Center

Dr. David Wynes, Emory University School of Medicine
Dr. Gary Chadwick, MPH, University of Rochester, School of Medicine and Dentistry
Dr. Jorge Jose, Indiana University School of Medicine
Ms. Nancy J. Lee, Stanford University School of Medicine
Dr. John L. Bixby, University of Miami, Miller School of Medicine
Dr. Hilary H. Ratner, Wayne State University
Dr. James C. Walker, University of Iowa
Dr. Andrew Rudczynski, Yale University School of Medicine
Dr. Gary S. Firestein, University of California, San Diego
Dr. Daniel L. Gross, Sharp Mary Birch Hospital for Women and Newborns
Dr. Paul B. Roth, University of New Mexico Health Sciences Center

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

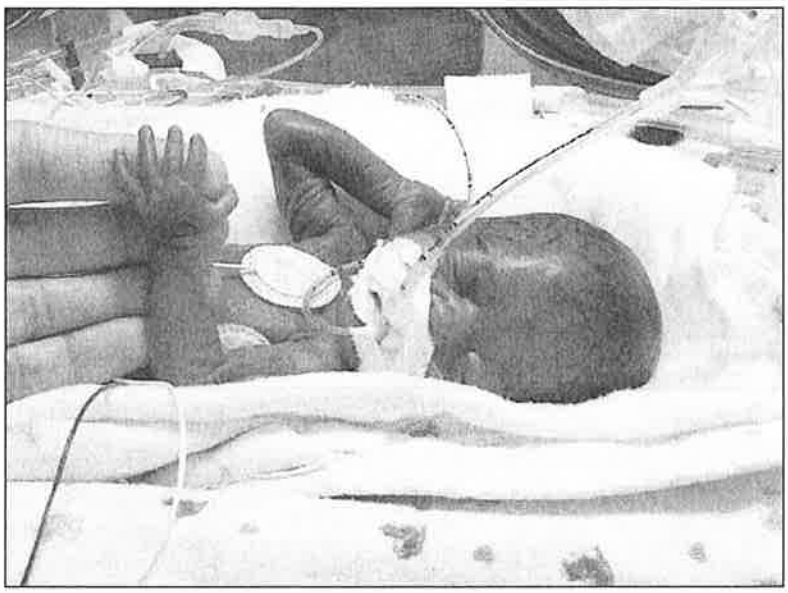
In Support of SUPPORT — A View from the NIH

Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

Each year in the United States, nearly 500,000 infants — 1 in every 8 — are born prematurely, before 37 weeks of gestation. Despite substantial advances in their care, premature infants face a daunting array of challenges; they are at high risk for death in infancy and face severe and lifelong health problems if they survive.[1] The National Institutes of Health (NIH) has a legal and moral responsibility to do research in partnership with scientists and families to optimize the care of these highly vulnerable infants. In recent weeks, a major public debate has arisen regarding a study designed to do just that. And the ramifications go well beyond this one study: the outcome of this debate could affect how we conduct and communicate about critical research on interventions that are within the standard of care for all diseases and conditions.

The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), carried out at more than 20 sites between 2004 and 2009, sought to identify, in infants born very prematurely at 24 to 27 weeks' gestation, the oxygen-saturation level within the range considered the standard of care that would minimize the risk of retinopathy of prematurity (ROP), a complication of oxygen therapy that can result in vision loss.[2] When the study began, targeting an oxygen-saturation range of 85 to 95% was becoming standard clinical practice, and the American Academy of Pediatrics (AAP) later recommended this range in its 2007 guidelines. The SUPPORT researchers and institutional review boards (IRBs), practicing clinicians, and the AAP had no scientific evidence to expect a difference in mortality between the two treatment groups in SUPPORT — one with the oxygen saturation target of 85 to 89%, the other with the target of 91 to 95%.

An important finding of the study was a reduced incidence of ROP in the lower oxygen-saturation range. However, contrary to what was known at the time, the study also showed a slightly but significantly increased incidence of death — 19.9% versus 16.2% (P=0.04) — among infants assigned to the lower as compared with the upper range. As a result, last year the AAP amended its guidelines, citing SUPPORT, and physicians treating very premature infants are starting to use higher saturation rates to reduce the risk of death, even with the potentially higher risk of ROP at these levels. Studies such as SUPPORT that compare two alternatives, both within current standard clinical practice, often lead to critical improvements in medical care.



A 400-Gram Female Infant Delivered at 24 and 4/7 Weeks.

The federal Office for Human Research Protections (OHRP), which is charged with providing leadership in the protection of the rights, welfare, and well-being of persons involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS), asserted in March 2013, on the basis of its own examination of the evidence, that the SUPPORT researchers failed to provide prospective parents sufficient information about the risks posed by the study. After a detailed review of the protocol, the relevant consent documents, and the research literature, we respectfully disagree with the conclusions of the OHRP, which we believe resulted from a fundamental difference in interpretations of how the regulations should apply to the state of scientific understanding when the SUPPORT study commenced. Moreover, there is a larger issue here: how risks should be conveyed in the informed-consent process when research is comparing interventions that are all considered to be the standard of care.

In a letter dated March 7, 2013, the OHRP asserted that the study's consent form failed to convey that "the level of oxygen being provided to some infants, compared to the level they would have received had they not participated, could increase the risk of brain injury or death."[3] That finding was influenced by research conducted in the 1950s, but in our view, it failed to assign proper weight to studies conducted in premature infants in the 2000s, which used more sophisticated oxygen-monitoring and oxygen-measurement devices, similar to those used in SUPPORT.[4] The more recent studies showed no increased risk of death or neurodevelopmental impairment at saturation levels as low as 70%.[5]

Given these data, the investigators had no reason to foresee that infants in one study group would have a higher risk of death than would those in the other group. The babies included in SUPPORT were, of course, facing substantial risks because of prematurity — the same risks as premature babies who were not enrolled in the study — but their care was never compromised for the sake of the study. The sample consent form for SUPPORT stated that each of the "possible combinations of treatments is considered by some units to represent their desired approach" (www.nih.gov/icd/od/foia/library/Records.htm). This statement describes the clinical equipoise at the time of the study, which was, in fact, the justification for conducting a clinical trial. Although the OHRP took issue with the consent form, it stated that the study design was ethical — a conclusion worth emphasizing. The increased risk of death was a significant and unexpected finding of the study; if it had been known before the study began, standard clinical care would not have encompassed the lower oxygen range, and it would have been unethical to conduct the study.

The NIH is committed to ensuring that prospective research participants — and the people who speak for and love them — are given clear, complete, and accurate information about the risks and benefits of participating in research. We are strongly committed to supporting critical research studies like SUPPORT, which inform clinical care by providing rigorous evidence for use in daily practice. This controversy has alarmed some of the parents of infants who were in the study, confused the biomedical research community, and befuddled IRBs. Several other studies seeking new insights to improve care for these vulnerable infants have been put on hold as the field tries to understand the OHRP findings.

But controversies such as this are also an opportunity to advance shared understanding, provide clarification, and encourage progress. The public debate sur-

rounding the SUPPORT study has set the stage for a substantive national dialogue with the research, advocacy, and ethics communities on how best to respect and protect participants in research studies conducted within the standard of care and how to define "reasonably foreseeable risks" in this setting. The timing is critical — the clinical research community, bioethicists, regulators, IRBs, and prospective research participants are paying close attention now. The NIH is happy to work with all stakeholders to advance this important dialogue and its translation into clear guidance, in accordance with the plan just announced by the DHHS (www.hhs.gov/ohrp/). In addition, a new letter to the University of Alabama at Birmingham from the OHRP, stating its intention to put all compliance actions on hold until the process of producing appropriate guidance is completed, is available now on the OHRP website (www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf).

Going forward, the NIH strongly and unequivocally supports the importance of the role of the OHRP in the oversight of human subjects research. But the community will benefit from an explicit description of the process the OHRP follows for investigating complaints. For example, when questions are raised about reasonably foreseeable risks and the state of the science relevant to a particular clinical trial, appropriate independent experts might need to be consulted. Finally, we are pleased to see the DHHS plans to ensure that investigators and IRBs will have a fair and transparent process for appealing OHRP findings and compliance actions, in those situations in which reasonable people disagree about the actions taken.

The circumstances surrounding the SUPPORT study have unquestionably created controversy in the research community, but the situation has created an opportunity for a better understanding of the scientific and ethical issues that must be addressed when designing such studies in the future. We look forward to working with the OHRP, the research community, and patient advocates to improve the effectiveness and ethical standards of research involving human participants.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the National Institutes of Health, Bethesda, MD.

This article was published on June 5, 2013, at NEJM.org.

1. Martin JA, Hamilton BE, Ventura SJ, Osteman MJK, Wilson EC, Mathews TJ. Births: final data for 2010. Natl Vital Stat Rep 2012;61(1):1-71 (http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_01.pdf).
2. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-69.
3. Determination Letter from the Office for Human Research Protections to University of Alabama at Birmingham. March 7, 2013 (http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf)
4. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003;111:339-45.
5. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-F110.

DOI: 10.1056/NEJMp1306986

Bartok, Lauren (NIH/OD) [C]

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Monday, July 22, 2013 2:45 PM
To: Lewis, Caya (HHS/IOS)
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: Final QFR
Attachments: nih comments on oash revision 7-21.docx

Follow Up Flag: Follow up
Flag Status: Completed

Hi Caya -

So sorry you weren't cc'd. Here is the version with NIH edits. Kathy sent this at 12:46 (see below) and this is the version that Norris is commenting on in his email from 12:58 PM this afternoon.

Best,
Steph

-----Original Message-----
From: Lewis, Caya (HHS/IOS)
Sent: Monday, July 22, 2013 2:31 PM
To: Cochran, Norris (HHS/ASFR); Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Do we have suggested edits from NIH to the draft Wanda sent around?

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 2:09 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: Re: Final QFR

Thank you, Kathy. If you have them handy, please send me her public statements

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 02:04 PM
To: Cochran, Norris (HHS/ASFR); Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS)
Subject: RE: Final QFR

I will of course defer to ASFR on what direction to take (b)(5)

(b)(5)

(b)(5)

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 12:58 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

(b)(5)

(b)(5)

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 12:46 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

I sent you a wrong version of our edits.

Can you take a look at this version please?

Sorry I had attachment problems.

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, July 21, 2013 12:37 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Wanda, Howard, Jerry,

Thanks for taking another stab at the Shelby QFR response. (b)(5)

(b)(5)

Please let me know what you think of this proposed revision.

Thanks
Kathy

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Friday, July 19, 2013 4:28 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Fw: Final QFR

Kathy - Please see below and attached. Please let me know of any major issues as soon as you can. Thank you.

Norris

----- Original Message -----
From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Friday, July 19, 2013 04:21 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Grifka, Michelle (HHS/OASH); Gannon, Jennifer (HHS/ASFR)
Subject: Final QFR

Norris, We have taken language exactly from the (second) letter sent to UAB, except that we've added a regulatory citation that was implicit in the letter's reference to what 'society requires'; in this particular context, that might not be so obvious.

If you have any questions, don't hesitate to reach out to me. Wanda

Wanda K. Jones, Dr.P.H.
Principal Deputy Assistant Secretary for Health US Department of Health and Human Services
200 Independence Ave. SW, Room 716G
Washington, DC 20201
Phone 202 260 4432
Main 202 690 7694
Fax 202 690 6960
Email wanda.jones@hhs.gov

"Mobilizing leadership in science and prevention for a healthier nation"

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Bartok, Lauren (NIH/OD) [C]

From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, July 22, 2013 1:22 PM
To: Cochran, Norris (HHS/ASFR); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: Final QFR

Follow Up Flag: Follow up
Flag Status: Completed

Norris, you've cut right to the chase. We'd suggest a relatively minor clarification of the response to #1:

"The specific scientific data that existed at the start of the study that shows an increased risk are described in the articles cited in a letter dated June 4, 2013, from OHRP to the University of Alabama, which can be found on OHRP's web site at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf."

So, #1 would now be as follows:
****
1. Could you please provide the specific scientific data that existed at the start of the study that shows this increased risk?

Response:

The specific scientific data that existed at the start of the study that shows an increased risk are described in the articles cited in a letter dated June 4, 2013, from OHRP to the University of Alabama, which can be found on OHRP's web site at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf.
****

If this is acceptable to all, we may be done. Thanks. Wanda

//////////////////////
-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 12:58 PM
To: Hudson, Kathy (NIH/OD) [E]; Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

(b)(5)

(b)(5)

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, July 22, 2013 12:46 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

I sent you a wrong version of our edits.

Can you take a look at this version please?

Sorry I had attachment problems.

-----Original Message-----

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, July 21, 2013 12:37 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Wanda, Howard, Jerry,

Thanks for taking another stab at the Shelby QFR response. (b)(5)

(b)(5)

Please let me know what you think of this proposed revision.

Thanks
Kathy

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Friday, July 19, 2013 4:28 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Fw: Final QFR

Kathy - Please see below and attached. Please let me know of any major issues as soon as you can. Thank you.

Norris

----- Original Message -----
From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Friday, July 19, 2013 04:21 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Grifka, Michelle (HHS/OASH); Gannon, Jennifer (HHS/ASFR)
Subject: Final QFR

Norris, We have taken language exactly from the (second) letter sent to UAB, except that we've added a regulatory citation that was implicit in the letter's reference to what 'society requires'; in this particular context, that might not be so obvious.

If you have any questions, don't hesitate to reach out to me. Wanda

Wanda K. Jones, Dr.P.H.
Principal Deputy Assistant Secretary for Health US Department of Health and Human Services
200 Independence Ave. SW, Room 716G
Washington, DC 20201
Phone 202 260 4432
Main 202 690 7694
Fax 202 690 6960
Email wanda.jones@hhs.gov

"Mobilizing leadership in science and prevention for a healthier nation"

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, July 22, 2013 12:45 PM
To: Cochran, Norris (HHS/ASFR)
Subject: Final QFR

I sent the wrong version of the qfr. (b)(5)
(b)(5)

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Monday, July 22, 2013 12:44 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: Final QFR

Kathy - we will work to get the revised into the record in lieu of the earlier draft absent hearing soon there are any remaining open issues.

-----Original Message-----
From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Monday, July 22, 2013 12:22 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS); Bumpus, Kirby (HHS/OASH)
Subject: RE: Final QFR

All, here's the final version, per my discussion just now with Norris. Because OHRP has regulatory authority of the Department, the answer to question 2 that Kathy supplied has been modified to the 'editorial we'. Wanda

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From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Sunday, July 21, 2013 12:37 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
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Thanks for taking another stab at the Shelby QFR response. (b)(5)
(b)(5)

Please let me know what you think of this proposed revision.

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Subject: Fw: Final QFR

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Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]; Lewis, Caya (HHS/IOS); Bumpus, Kirby (HHS/OASH)
Subject: Final QFR
Attachments: Final QFR 7-22-13.docx

Follow Up Flag: Follow up
Flag Status: Completed

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(b)(5)

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SUPPORT Clinical Trial

The University of Alabama at Birmingham (UAB) recently received a letter from the Office for Human Research Protections (OHRP) about the SUPPORT clinical trial, a research study of premature infants and supplemental oxygen. In the letter, OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study.

1. Could you please provide the specific scientific data that existed at the start of the study that shows this increased risk?

Response:
The SUPPORT investigators did not design the study with the expectation that they would find a difference in mortality rates between the high and low oxygen groups. Whereas much earlier studies of oxygen supplementation in premature babies had shown risks of mortality and neurological damage at very low oxygen levels, more recent studies did not demonstrate such risks. Consequently, when the SUPPORT study was initiated, there was no clear recent evidence indicating that different oxygenation levels with the then-current standard of care (85%-95%) would produce differences in neurological damage or survival.

The medical profession looks at many factors when assessing potential risks. At the outset of the SUPPORT study, many in the research and clinical communities remained concerned about the possible relationship between low oxygen and increased mortality and neurodevelopmental problems within the oxygen ranges that were to be evaluated in that study. Indeed, such concerns were a core reason why the study was conducted. Those concerns were sufficient to affect clinical decisions and discouraged some doctors from treating premature infants at lower oxygen levels.

Indeed, descriptions of the process of designing the SUPPORT study and four similar studies conducted in other countries indicate a clear awareness of such concerns and the need to resolve them. This is evidenced by multiple statements from the SUPPORT investigators and other experts, who identified the important need for a large randomized study with sufficient power to detect differences in mortality rates of 5% or greater. The information that both clinicians and researchers relied upon in determining that there was a possible risk of increased mortality is explained in the articles cited in a letter dated June 4, 2013, from OHRP to the University of Alabama, which can be found on OHRP's web site at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf.

2. If no such data existed, could you please explain why it would be scientifically credible or ethical to explain unknown risks of a study?

Response:

As noted in the answer to question 1, we believe that such data did indeed exist. HHS does not and has never questioned whether the design of the SUPPPORT study was ethical.

3. What is the process for appealing the findings of OHRP? Is there a mechanism for having an independent review of OHRP actions especially when they are so universally called into question as in this case? (Please see, for example, editorials and correspondence in the New England Journal of Medicine and The Hastings Center Bioethics Forum).

Response:

OHRP's compliance oversight procedures state that an institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation, http://www.hhs.gov/ohrp/compliance/evaluation/index.html. OHRP has no recollection of any such requests for reconsideration from an institution against which OHRP made a determination of noncompliance. Historically, OHRP has received such requests only from complainants concerned that OHRP did not agree with their allegations of noncompliance. If such complainants are unsatisfied with the response of the OHRP Director, OHRP informs them that they may communicate with the Principal Deputy Assistant Secretary for Health and the Assistant Secretary for Health and ask them to review the matter.

Bartok, Lauren (NIH/OD) [C]

Subject: Conferenc Call with Dr. Howard Koh re: SUPPORT Study
Location: 1/103 - We will call him at 202-690-7694

Start: Wed 7/17/2013 5:00 PM
End: Wed 7/17/2013 5:30 PM

Recurrence: (none)

Categories: Phone Call

Porter, Kevin (NIH/OD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, July 21, 2013 12:39 PM
To: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: FW: Final QFR
Attachments: nih comments on oash revision 7-21.docx

This is proving difficult...

-----Original Message-----
From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, July 21, 2013 12:37 PM
To: Jones, Wanda K. (DHHS/OS/OASH); Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH)
Cc: Cochran, Norris (HHS/ASFR); Devaney, Stephanie (NIH/OD) [E]
Subject: RE: Final QFR

Wanda, Howard, Jerry,

Thanks for taking another stab at the Shelby QFR response. Th(b)(5)

(b)(5)

Please let me know what you think of this proposed revision.

Thanks
Kathy

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Friday, July 19, 2013 4:28 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Fw: Final QFR

Kathy - Please see below and attached. Please let me know of any major issues as soon as you can. Thank you.

Norris

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From: Jones, Wanda K. (DHHS/OS/OASH)
Sent: Friday, July 19, 2013 04:21 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Grifka, Michelle (HHS/OASH); Gannon, Jennifer (HHS/ASFR)
Subject: Final QFR

Norris, We have taken language exactly from the (second) letter sent to UAB, except that we've added a regulatory citation that was implicit in the letter's reference to what 'society requires'; in this particular context, that might not be so obvious.

If you have any questions, don't hesitate to reach out to me. Wanda

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Washington, DC 20201
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"Mobilizing leadership in science and prevention for a healthier nation"

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Bartok, Lauren (NIH/OD) [C]

From: Cochran, Norris (HHS/ASFR)
Sent: Sunday, July 21, 2013 9:47 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Final QFR

Follow Up Flag: Follow up
Flag Status: Completed

(b)(5)

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Sunday, July 21, 2013 09:28 AM
To: Cochran, Norris (HHS/ASFR)
Subject: Re: Final QFR

(b)(5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov

On Jul 19, 2013, at 4:27 PM, "Cochran, Norris (HHS/ASFR)" <Norris.Cochran@HHS.GOV> wrote:

> Kathy - Please see below and attached. Please let me know of any major issues as soon as you can. Thank you.
>
> Norris
>
> ----- Original Message -----
> From: Jones, Wanda K. (DHHS/OS/OASH)
> Sent: Friday, July 19, 2013 04:21 PM
> To: Cochran, Norris (HHS/ASFR)
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>
> <Shelby question draft answer 3 - clean.docx>

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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(b)(5)

of the Freedom of Information and Privacy Act

Bartok, Lauren (NIH/OD) [C]

From: Cochran, Norris (HHS/ASFR)
Sent: Thursday, July 18, 2013 5:30 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: do you have memo

(b)(5)

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, July 18, 2013 1:14 PM
To: Cochran, Norris (HHS/ASFR)
Subject: RE: do you have memo

(b)(5)

From: Cochran, Norris (HHS/ASFR)
Sent: Thursday, July 18, 2013 1:12 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Re: do you have memo

Excellent, thank you! I don't, but will try to get it.

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, July 18, 2013 01:08 PM
To: Cochran, Norris (HHS/ASFR)
Subject: do you have memo

(b)(5)

I am on the trail.

Kathy (aka bloodhound) Hudson

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, July 17, 2013 10:58 PM
To: Lewis, Caya (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]; Shapiro, Neil (NIH/OD) [E]; Cochran, Norris (HHS/ASFR)
Subject: QFR on SUPPORT
Attachments: QFR with nih redline.docx

Caya,

Yesterday we received a note from a grantee institution sharing with us a copy of a QFR from the Secretary's hearing before Senate Approps Cmte. We had not previously seen this QFR or been asked to clear.

(b)(5)

Thanks
kathy

From: Devaney, Stephanie (NIH/OD) [E]
Sent: Wednesday, July 17, 2013 7:39 PM
To: Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH)
Cc: Hudson, Kathy (NIH/OD) [E]
Subject: QFR on SUPPORT

Good evening –

Kathy asked me to send along NIH's mark-up of the SUPPORT QFR. This is the version Kathy sent to ASFR today.

Best regards,
Stephanie

Stephanie Devaney, Ph.D.

Science Policy Analyst
Special Assistant to the Deputy Director for Science, Outreach, and Policy
Office of the Director
National Institutes of Health
1 Center Drive, Building 1/103
Bethesda, MD 20892
Phone: 301-402-1994
stephanie.devaney@nih.gov

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

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(b)(5)

of the Freedom of Information and Privacy Act

Bartok, Lauren (NIH/OD) [C]

From: Cochran, Norris (HHS/ASFR)
Sent: Wednesday, July 17, 2013 10:31 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: SUPPORT study QFR with nih redline

Follow Up Flag: Follow up
Flag Status: Completed

Yes, that works. Thank you, Kathy.

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, July 17, 2013 10:28 PM
To: Cochran, Norris (HHS/ASFR)
Subject: RE: SUPPORT study QFR with nih redline

Thank you. Just fyi, (b)(5)

(b)(5)

-----Original Message-----
From: Cochran, Norris (HHS/ASFR)
Sent: Wednesday, July 17, 2013 10:00 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Re: SUPPORT study QFR with nih redline

Thank you, Kathy. On the Q+A we'll ask OASH to clear it and then I'll engage the Committee on options. On NCI, it should be quick, I could try you in the morning again, if that's okay.

----- Original Message -----
From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, July 17, 2013 09:50 PM
To: Cochran, Norris (HHS/ASFR)
Subject: Re: SUPPORT study QFR with nih redline

(b)(5)

What are next steps?

(b)(5)

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy NIH
301 496 1455
kathy.hudson@nih.gov<mailto:kathy.hudson@nih.gov>

On Jul 17, 2013, at 7:26 PM, "Cochran, Norris (HHS/ASFR)"
<Norris.Cochran@HHS.GOV<mailto:Norris.Cochran@HHS.GOV>> wrote:

Kathy – did you and Dr. Koh connect and reach agreement on wording for the Q+A today?

(b)(5)

Thank you!

Norris

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, July 17, 2013 1:47 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Devaney, Stephanie (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Shapiro, Neil (NIH/OD) [E]
Subject: RE: SUPPORT study QFR with nih redline

I think our desired response is the redline. The comment bubbles is our commentary….

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Thank you, Kathy. (b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, July 17, 2013 12:42 PM
To: Cochran, Norris (HHS/ASFR)
Cc: Devaney, Stephanie (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Shapiro, Neil (NIH/OD) [E]
Subject: SUPPORT study QFR with nih redline

Norris,

As quick background, (b)(5)

(b)(5)

Thanks
kathy

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(b)(5)

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(b)(5)

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(b)(5)

Kathy Hudson, Ph.D.
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kathy.hudson@nih.gov<mailto:kathy.hudson@nih.gov>

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<Norris.Cochran@HHS.GOV<mailto:Norris.Cochran@HHS.GOV>> wrote:

Kathy – did you and Dr. Koh connect (b)(5)

Separately, when there is time tomorrow I would like to catch up with you on (b)(5)
(b)(5)

Thank you!

Norris

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(b)(5)

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Cc: Devaney, Stephanie (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Shapiro, Neil (NIH/OD) [E]
Subject: SUPPORT study QFR with nih redline

Norris,

As quick background, (b)(5)

(b)(5)

Thanks
kathy

Butler, Brenda (NIH/OD) [E]

From: Cochran, Norris (HHS/ASFR)
Sent: Wednesday, July 17, 2013 12:03 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Question about QFR - NIH concerns about response to senate

Kathy - let's talk in the morning. If we had a break down in the review process, I apologize. It will help to know the specific problems with the below responses for any follow up.

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Tuesday, July 16, 2013 11:16 PM
To: Cochran, Norris (HHS/ASFR)
Subject: Question about QFR - NIH concerns about response to senate

Norris,

Given we did not connect tonight, let me pose my question by email.

(b)(5)

Can you help me out? Also, can you tell me when the qfrs were actually delivered to the senate?

Thanks Norris.

kathy

SUPPORT Clinical Trial

The University of Alabama at Birmingham (UAB) recently received a letter from the Office for Human Research Protections (OHRP) about the SUPPORT clinical trial, a research study of premature infants and supplemental oxygen. In the letter, OHRP determined that UAB should have informed parents of an increased risk of death of their infant by participating in the study.

1. Could you please provide the specific scientific data that existed at the start of the study that shows this increased risk?

Response:

At the time the SUPPORT study began, substantial information was available on possible risks of increased mortality at lower oxygen levels. In 2003, an international group of over 30 experts began a collaboration around improving the understanding of neonatal oxygenation through well-designed clinical trials. One output of this nascent collaboration was a 2003 commentary in Pediatrics (Cole et al., Resolving Our Uncertainty

About Oxygen Therapy, Pediatrics 2003;112:1415), which discussed many aspects of what such studies should involve. They noted, for example, that a large sample would be needed to "exclude smaller, important differences in outcomes such as mortality and disability to address real concerns about the safety of lower oxygen tensions." This information, and other similar concerns, is more fully described in the letter dated June 4, 2013, from OHRP to the University of Alabama, which can be found on OHRP's web site at http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf.

2. If no such data existed, could you please explain why it would be scientifically credible or ethical to explain unknown risks of a study?

Response:
At the time the SUPPORT study began, substantial information was available on possible risks of increased mortality at lower oxygen levels.

3. What is the process for appealing the findings of OHRP? Is there a mechanism for having an independent review of OHRP actions especially when they are so universally called into question as in this case? (Please see, for example, editorials and correspondence in the New England Journal of Medicine and The Hastings Center Bioethics Forum).

Response:
OHRP's compliance oversight procedures state that an institution or complainant may request that the Director of OHRP reconsider any determinations resulting from a for-cause compliance oversight evaluation, http://www.hhs.gov/ohrp/compliance/evaluation/index.html. OHRP has no recollection of any such requests for reconsideration from an institution against which OHRP made a determination of noncompliance. Historically, OHRP has received such requests only from complainants concerned that OHRP did not agree with their allegations of noncompliance. If such complainants are unsatisfied with the response of the OHRP Director, OHRP informs them that they may communicate with the Principal Deputy Assistant Secretary for Health and the Assistant Secretary for Health and ask them to review the matter.

Laura Friedel
Committee on Appropriations
Subcommittee on Labor, HHS and Education
156 Dirksen Senate Office Building
Washington, DC 20510
202-224-0314

Bartok, Lauren (NIH/OD) [C]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Monday, July 01, 2013 9:18 PM
To: Lewis, Caya (HHS/IOS)
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: more on support

http://www.bmj.com/content/346/bmj.f3786

main article here. click on tab above title to see responses to the article.

Kathy L. Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
National Institutes of Health

301 496 1455
Kathy.hudson@nih.gov

Celebration of Science at NIH: *watch how medical research saves lives and improves health*

BMJ Open Respiratory Research

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Editorial

How not to reduce uncertainties in care

BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f3786 (Published 12 June 2013)
Cite this as: BMJ 2013;346:f3786

Neena Modi, professor of neonatal medicine

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US Office for Human Research Protections messes up

The randomised controlled trial has justifiably been embraced as necessary to the delivery of evidence based medicine. Randomisation reduces confounding by unknown factors, ensures every patient has a fair and equal chance of receiving the best (as yet unknown) treatment option, and is the gold standard approach to identifying effective treatments for future patients. In an ideal world every treatment uncertainty would be dealt with in this way. Recent experience in the United States highlights the unexpected barriers to doing this.

Most uncertainties in healthcare relate not to new experimental treatments but to those already in wide use. The administration of oxygen to premature babies is an example of this. A longstanding uncertainty about the treatment—the optimum saturation target—was put to the test of a randomised controlled trial. Preterm babies with respiratory immaturity often need additional oxygen, but too much oxygen is associated with a proliferative retinal vasculopathy—retinopathy of prematurity—a cardinal cause of lifelong visual impairment and blindness. For this reason, the accepted standard of care oxygen saturation range of 85 -95% is used to avoid levels that are too low or too high.

Investigators in the United Kingdom, Australia, New Zealand, and the US set about designing a randomised controlled trial to refine this range and determine whether targeting the lower end of the accepted range (85-89%), rather than the upper end (91 -95%), reduced the incidence of retinopathy of prematurity. The US SUPPORT trial found that babies given oxygen at the higher end of the recommended range did have a greater incidence of retinopathy of prematurity, but, unexpectedly, babies at the lower end had a higher risk of death.1 The data monitoring committees of the UK, Australian, and New Zealand BOOST2 trials reviewed interim data, confirmed the higher risk of death in babies randomised to the lower saturation range, and stopped further recruitment.2

These trials recruited thousands of babies and advanced knowledge and preterm care, yet in March 2013 the lead investigators for the SUPPORT trial received a letter from the Office for Human Research Protections informing them that they were "in

violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage, and death."3 A commentary in the *New England Journal of Medicine* pointed out that the SUPPORT consent form, approved by no less than 23 US institutional review boards, explained the prevalent equipoise and state of knowledge "fairly and reasonably."4 The higher risk of death at the lower saturation range would never have been recognised had it not been for the SUPPORT trial. Finding researchers at fault for not foreseeing an unexpected outcome and suggesting that babies were at greater risk from randomisation when they received oxygen within accepted standard of care limits has led to confusion and mistrust among parents and the public. It has also set back attempts to reduce treatment uncertainties.5

As with all sciences, there are no absolute truths in medicine, only a progressive reduction in uncertainty with each null hypothesis rejected. Illogical regulation, as reflected in this response, and poor integration of research with day to day clinical practice delay the incremental advances that are essential to improve care. To redress this, a paradigm shift is needed, involving acceptance of randomised allocation of treatments already widely used as a standard of care, an approach that has been used successfully in developing treatment protocols in oncology. Continuing uncertainty will ultimately result in many more patients being disadvantaged or harmed by receiving the (unknown) worse treatment. It is also noteworthy that infants in both higher and lower saturation target arms of the SUPPORT trial had a lower rate of death than infants who were not enrolled. It is time to be honest and tell patients and parents that the fairest chance of receiving the (unknown) best treatment is through randomisation because the choice of treatment is not affected by clinician bias. There is also likely to be benefit, regardless of allocation arm, from participating in methodologically rigorous comparisons of standard treatments, because care will be delivered along a closely monitored pathway.

In adopting this approach, peer review and explanation would remain unchanged. The involvement of patients can help ensure that the design of comparisons is acceptable and explained clearly, and regulatory approval should be proportionate. The key difference is that randomisation would be the recommended default and that patients would be offered the opportunity to opt out, rather than invited to opt in. This would reduce the burden of decision making at difficult and stressful times. It would also reduce the risk of "injurious misconception," where participation is inappropriately rejected because of an exaggerated and disproportionate perception of risk,6 and speed up trial completion. Data can increasingly be extracted from electronic clinical records, reducing costs and the burden on busy clinical teams.7 This approach would fulfil the four cardinal principles of research ethics—autonomy, justice, beneficence, and non-maleficence—and uphold the responsibility enshrined in General Medical Committee guidance that doctors must "strive to reduce uncertainties in care."8

Notes

Cite this as: *BMJ* 2013;346:f3786

Footnotes

- Competing interest statement: I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: I am chair of the BMJ Ethics Committee, chair of the Royal College of Paediatrics and Child Health "Updating Guidance for Children's Researchers" working party, and a clinical academic conducting research involving patients and healthy volunteers.

- Provenance and peer review: Commissioned; not externally peer reviewed.

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1. ↵

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CrossRefMedline

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CrossRefMedlineWeb of Science

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4. ↵
Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. N Engl J Med2013;368:1929-31.
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5. ↵
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BMJ Open Respiratory Research

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Editorial

How not to reduce uncertainties in care

BMJ 2013; 346 doi: http://dx.doi.org/10.1136/bmj.f3786 (Published 12 June 2013)
Cite this as: BMJ 2013;346:f3786

Recent rapid responses

Rapid responses are electronic letters to the editor. They enable our users to debate issues raised in articles published on bmj.com. Although a selection of rapid responses will be included as edited readers' letters in the weekly print issue of the BMJ, their first appearance online means that they are published articles. If you need the url (web address) of an individual response, perhaps for citation purposes, simply click on the response headline and copy the url from the browser window.

Re: How not to reduce uncertainties in care

1 July 2013

Exposure of the decision of the Office for Human Research Protection (OHRP) to investigate and then challenge the lead investigators of the SUPPORT trial that they failed to meet the regulatory informed consent requirements [1] brought both vigorous and thoughtful support for SUPPORT [2][3] but also a defence [4] for the regulatory body`s untimely and damaging challenge in March 2013.

The stage has thus been set, as the NIH foresaw [2], by providing "an opportunity to advance shared understanding, provide clarification, and encourage progress" for a public debate for "a substantive national dialogue with the research, advocacy, and ethics communities on how best to respect and protect participants in research studies conducted within the standard of care and how to define `reasonable foreseeable risks` in this setting."

The benefits of involvement of patients and citizens in the research process have become increasingly recognised in the decade since the SUPPORT study was conceived and initiated. Many initiatives since then to educate the public about research concepts have begun to produce better-informed citizens and better-informed health professionals. [5] I concur with Neena Modi`s assertion [3] that "involvement of patients can help to ensure that the design of comparisons is acceptable and explained clearly".

Enough damage has been done by undue focus and insistence on retrospective precise adherence to regulatory requirements, but failing to take into account the harm it is causing by over-zealous morale-sapping fault finding to the exclusion of all else. That the consent process fell short of the ideal has been acknowledged by both groups of `experts`. Is it not time to move forward to use this debate to bring about more satisfactory ways of achieving `informed concordance` [6] between health professionals and those from whom they seek consent, and for their becoming thoroughly involved in reducing the many uncertainties in the way that healthcare is provided?

"The timing is critical": everyone is "paying close attention now". [2] It is a time, surely, to consider the spirit of the law as well as the letter of the law? We must ensure that the endeavours of the clinicians and trial participants in the SUPPORT Trial will not have been in vain.

REFERENCES:

[1]] Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. N. Engl. J. Med. 2013;368(20):1929-31.

[2] Hudson KL, Guttmacher AE, Collins FS. In Support of SUPPORT - A View from the NIH. N. Engl. J. Med. 2013. DOI: 10.1056/NEJMp1306986
[3] Modi N. How not to reduce uncertainties in care. US Office for Human Research Protection messes up. Br. Med. J. 2013;346:f3786
[4] Macklin R, Shepherd JD, Dreger A, et al. The OHRP and SUPPORT – Another View. N Eng J Med 2013; DOI: 10.1056/NEJMc1308015
[5] Evans I, Thornton H, Chalmers I, Glasziou P. Testing treatments: better research for better healthcare – Second Edition. Pinter and Martin, London. 2011. ISBN 978-1-905177-48-6 Free download from www.ncbi.nlm.nih.gov/books/nbk66204/
[6] Thornton H. Informed consent in the management and research of breast cancer. In: Benson JR, Gui G, Tuttle TM. Early Breast Cancer: from screening to multidisciplinary management. Third edition, CRC Press, Taylor and Francis Group, Boca Raton, USA. (2013) pp 328-340.

Competing interests: None declared

Hazel Thornton, Honorary Visiting Fellow, Department of Health Sciences
None
University of Leicester, "Saionara", 31 Regent Street, Rowhedge, Colchester, CO5 7EA

Re: How not to reduce uncertainties in care

14 June 2013

The shortcomings and the harmful after-effects of the ill-conceived intervention by the Office for Human Research Protection (OHRP) in challenging the running of the SUPPORT trial have been overlooked in Pharoah`s defence of their action. [1] The OHRP`s assertion that the investigators were "in violation of the regulatory requirements for informed consent" was illogical because it failed to properly understand or appreciate the current state of uncertainty and regulation that obtained at the time the investigators set out to reduce it by conducting their study, as clearly described in Modi`s editorial. [2]
Furthermore, as the U.S. National Institutes of Health`s (NIH) "Support of SUPPORT" Perspective in the NEJM describes, [3] the OHRP failed to assign proper weight to more recent studies in its overview, those exploring effects of oxygen saturation levels as low as 70%. Yet this inadequacy in the OHRPS`s basis for challenging the investigators was overlooked by Pharoah when he selected this part of the evidence in his support for the OHRP`s action, and in his condemnation of widely-informed and well-reasoned support for SUPPORT from clinicians, governing organisations and journal editors. [2][3][4].
Pharoah`s explanation of his concept of equipoise and "one" (participants? investigators? both?) being required to trade-off "one harm against another" I find difficult to comprehend. This `Hobson`s choice" element is surely the dilemma that faces brave people confronted with addressing uncertainty about potential harms and benefits in studies?
This lack of appreciation by the OHRP of both the degree of uncertainty of ALL reliable evidence at the time the trial was conceived and approved and the manner of seeking consent prevailing at that time, together with their potential (now realised) for doing harm to all affected by this untimely wielding of authority - as well as the holding back of progress in reducing these uncertainties so that better-informed care can be provided - has been suitably addressed by various experienced and compassionate critics. [2][3][4][5][6]
The silver lining to this dark cloud is that this sorry tale of heavy-handed regulation is leading to many constructive suggestions for improvement to the regulation and governance of research including the consent process.

[1] Pharoah, P. Rapid response posted 13 June 2013 to Modi [2] http://www.bmj.com/content/346/bmj.f3786?tab=responses
[2] Modi N. How not to reduce uncertainties in care. US Office for Human Research Protection messes up. Br. Med. J. 2013;346:f3786
[3] Hudson KL, Guttmacher AE, Collins FS. In Support of SUPPORT - A View from the NIH. N. Engl. J. Med. 2013. DOI: 10.1056/NEJMp1306986
[4] Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. N. Engl. J. Med. 2013;368(20):1929-31.
[5] Magnus DR, Caplan AL. Risk, Consent, and SUPPORT. NEJM 2013; 368.20 p1864-65. DOI: 10.1056/NEJMp1305086
[6] Carlo WA, Bell EF, Walsh MC. Oxygen-Saturation Targets in Extremely Preterm Infants. N Eng.J. Med 368:20 p1949-50 DOI: 10.1056/NEJMc1304827

Competing interests: None declared

Hazel Thornton, Honorary Visiting Fellow, Department of Health Sciences
None
University of Leicester, "Saionara", 31 Regent Street, Rowhedge, Colchester, CO5 7EA

Re: How not to reduce uncertainties in care

13 June 2013

There has been substantial criticism of the findings of the investigation of the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services into the informed-consent process used when newborns were enrolled in SUPPORT [1-3]. The OHRP stated that the lead investigators were "in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage, and death". Critics have suggested that the judgment was flawed, has led to confusion and mistrust among parents and the public, and has set back attempts to reduce treatment and uncertainties.

Much of the criticism has focused on the fact that overall the risks (whatever those risks might be) to the premature baby would not be increased by taking part in the trial as the intervention in both arms of the trial were within usual care guidelines. This is not the key issue. The key issues are that the risks associated with being in one or other arm of the trial were likely to be different, that prior knowledge informed us what those differential risk might be, and that those giving consent to the trial should have been informed of those differential risks. They were not.

Before the SUPPORT trial it was known that low oxygen saturation was associated with poorer outcomes in terms of mortality and that higher oxygen saturations were associated with an increased risk of retinopathy of prematurity (ROP). What was not known was the shape of either of those dose response curves. And so, a trial was proposed in which the participants would be randomised into two groups according to managed oxygen saturation. Note that under these circumstances there is no clear concept of equipoise because one is trading off one harm against another. What constitutes equipoise will depend on the weight an individual puts on the two competing risks - one person's net benefit would be another person's net harm.

This trial only makes sense if there was uncertainty about the risks of both ROP and mortality in relation to managed oxygen saturation. Hudson and colleagues cited research showing that oxygen saturation levels as low as 70 per cent are not associated with an increased risk of death or neurological development [1]. If this were true and then there would have been no need for the trial as there could have been no conceivable harm to using the lower oxygen concentration and only a possible benefit - a lower incidence of ROP. The corollary of this is that standard clinical practice could not be justified and the trial would have been unethical as the criterion for equipoise would not have been met. And so we can only conclude that there was reasonable uncertainty about the association between oxygen saturation and mortality.

It was possible that those randomised to a higher oxygen saturation would have a higher incidence of ROP. This was known at the time the trial was started. Indeed, the parents were told about this possible differential risk as part of the informed consent. There was also a reasonable possibility that those randomised to a lower oxygen saturation would have a higher incidence of brain damage or mortality (as came to pass). However, parents were not told about this risk. Thus, the consent given by the parents could not be considered informed in any reasonable sense of the word.

One has to wonder why this information was not given to the parents. One explanation is that, given this information, parents may have opted out of the study and the very important data generated by this trial would not have been generated. This is not an acceptable reason for withholding information. The history of medicine and biomedical research is littered with examples of doctors and scientists withholding information from participants and justifying the withholding by the importance of the research question being addressed.

And so, the judgment of the OHRP seems entirely reasonable. If it has set back the conduct of studies aimed at reducing uncertainties in care then a debate and rethink about how such stuides are conducted is needed. In the SUPPORT study there seemed no good reason not to be clear and inform the parents of all the reasonably likely risks. If that had hampered recruitment into the trial then we would have to accept that this important clinical question cannot be answered be a randomised trial.

1. Hudson KL, Guttmacher AE, Collins FS. In Support of SUPPORT - A View from the NIH. N. Engl. J. Med. 2013.
2. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. N. Engl. J. Med. 2013;368(20):1929-31.

3. Modi N. How not to reduce uncertainties in care. Br. Med. J. 2013;346:f3786.

Competing interests: None declared

Paul D.P. Pharoah, Public Health Physician
University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, CB1 8RN

From: Guttmacher, Alan (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject: Re: FR notice re SUPPORT public meeting
Date: Monday, June 10, 2013 5:14:18 PM

Sounds right.

Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National institutes of Health

On Jun 10, 2013, at 4:22 PM, "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov> wrote:

> August 28th is the date.
>
> How should we share this info with NIH? Wait for notice and then send to tnbc, p&e, epmc, icd, and eieio?
>
> ---
>
> **From:** Lewis, Caya (HHS/IOS)
> **Sent:** Monday, June 10, 2013 2:14 PM
> **To:** Hudson, Kathy (NIH/OD) [E]
> **Subject:** FR notice re SUPPORT public meeting
>
> This is the final sent to OHRP
>
> <SUPPORT public meeting FR notice 6.5.13.doc>

Bartok, Lauren (NIH/OD) [C]

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, June 10, 2013 4:45 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: FR notice re SUPPORT public meeting

Thanks, Kathy. It's great to hear that. And if the briefing helps, we can see what else we can do to help people better understand the NPRM (and to revise it to make it clearer!).

Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, June 10, 2013 4:21 PM
To: Menikoff, Jerry (HHS/OASH)
Subject: RE: FR notice re SUPPORT public meeting

Great. Thanks.

Just finished reading the draft nprm. It looks terrific. thanks for doing the brfing tomorrow. I hope that will help smooth the final clearances.

From: Menikoff, Jerry (HHS/OASH)
Sent: Monday, June 10, 2013 4:07 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: RE: FR notice re SUPPORT public meeting

Kathy,

The date selected is August 28th, and yes, the notice has been put into the federal register process.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Monday, June 10, 2013 2:30 PM
To: Menikoff, Jerry (HHS/OASH)
Subject: FW: FR notice re SUPPORT public meeting

Hi Jerry
Caya forwarded this version of the fed reg notice. Do you know if a date has been selected and if the notice has been put into the fed reg process?

Thanks
kathy

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 10, 2013 2:14 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FR notice re SUPPORT public meeting

This is the final sent to OHRP

From:	Hudson, Kathy (NIH/OD) [E]
To:	Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]
Subject:	FW: FR notice re SUPPORT public meeting
Date:	Monday, June 10, 2013 4:22:28 PM
Attachments:	SUPPORT public meeting FR notice 6.5.13.doc

August 28th is the date.

How should we share this info with NIH? Wait for notice and then send to tnbc, p&e, epmc, icd, and eieio?

From: Lewis, Caya (HHS/IOS)
Sent: Monday, June 10, 2013 2:14 PM
To: Hudson, Kathy (NIH/OD) [E]
Subject: FR notice re SUPPORT public meeting

This is the final sent to OHRP

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Carr, Sarah (NIH/OD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Friday, May 10, 2013 10:42 AM
To: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Fwd: SUPPORT study
Attachments: 05 08 13 SUPPORT clarification b CLEAN.final version.docx; ATT00001.htm; 05 08 13 SUPPORT clarification .final version.docx; ATT00002.htm

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

From: "Koh, Howard (HHS/OASH)" <Howard.Koh@hhs.gov>
Date: May 8, 2013, 4:56:47 PM EDT
To: "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>, "Palm, Andrea (HHS/IOS)" <Andrea.Palm@hhs.gov>
Cc: "Corr, Bill (HHS/IOS)" <Bill.Corr@hhs.gov>, "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov>, "Schultz, William B (HHS/OGC)" <William.Schultz@hhs.gov>, "LaPan, Jarel (HHS/IOS)" <Jarel.LaPan@hhs.gov>, "Cheema, Subhan (HHS/IOS)" <Subhan.Cheema@hhs.gov>, "Horowitz, David (HHS/OGC)" <David.Horowitz@hhs.gov>, "Dotzel, Peggy (HHS/OGC)" <Peggy.Dotzel@hhs.gov>, "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>, "Guttmacher, Alan (NIH/NICHD) [E]" <guttmach@mail.nih.gov>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Wolters, Bradley (OS/OPHS)" <Bradley.Wolters@hhs.gov>
Subject: RE: SUPPORT study

Andrea and colleagues

Thank you for your feedback and these suggestions.

We now attach two versions of an updated document that slightly adjusts language further based on: 1) your comments and 2) Francis' email from this morning. One version now shows all redlined changes since the weekend;the other version is a clean copy. (b)(5)

(b)(5)

The specific responses to your suggestions are:

(b)(5)

(b)(5)

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]
Sent: Wednesday, May 08, 2013 5:34 AM
To: Palm, Andrea (HHS/IOS); Koh, Howard (HHS/OASH)
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC); Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT study

Dear Andrea,

Thanks for jumping in so effectively on this very complicated issue. We have made a few minor suggestions in the attached redlined document. (b)(5)

(b)(5)

This is OHRP's letter, and we appreciate their willingness to have our input to get to this point -- but this version of the letter should not be perceived as reflecting NIH's point of view.

While not ideal, I think it is okay for a Department that houses a research agency and regulatory bodies to have such disagreements from time to time.

We need to move on now to a more public discussion of these topics. Decisions about standards for consent for clinical trials within the standard of care affect vast swaths of NIH research. (b)(5)

(b)(5)

(b)(5) In addition, NIH will be planning a workshop in the very near future to discuss the scientific and ethical standards for conducting such studies. We will actively include OHRP in this workshop of course.

How do you like your new job so far? We at the NIH are thrilled to have you as the new Chief of Staff.

Best regards, Francis

From: Palm, Andrea (HHS/IOS)
Sent: Tuesday, May 07, 2013 1:06 PM
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Subject: SUPPORT study

Howard and Francis,

(b)(5)

Thanks again,
Andrea

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Carr, Sarah (NIH/OD) [E]

From: Hudson, Kathy (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 2:04 PM
To: Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: FW: SUPPORT study
Attachments: 05 07 13 SUPPORT clarificationAG.docx

See attached. (b)(5)

From: Guttmacher, Alan (NIH/NICHD) [E]
Sent: Tuesday, May 07, 2013 1:35 PM
To: Collins, Francis (NIH/OD) [E]; Hudson, Kathy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT study

(b)(5) After quick read, my comments on a couple of specific points are on the attached.

Alan

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, May 07, 2013 1:15 PM
To: Hudson, Kathy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT study

FYI, I've only scanned...

From: Palm, Andrea (HHS/IOS)
Sent: Tuesday, May 07, 2013 1:06 PM
To: Koh, Howard (HHS/OASH); Collins, Francis (NIH/OD) [E]
Cc: Corr, Bill (HHS/IOS); Lewis, Caya (HHS/IOS); Schultz, William B (HHS/OGC); LaPan, Jarel (HHS/IOS); Cheema, Subhan (HHS/IOS); Horowitz, David (HHS/OGC); Dotzel, Peggy (HHS/OGC)
Subject: SUPPORT study

Howard and Francis,

(b)(5)

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From: Rowe, Mona (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: RE: Preemie studies - heads up
Date: Sunday, May 05, 2013 3:41:14 PM

Confirming our first FOIA request- hope this helps, Mona

FOIA 1 from Public Citizen

The request is seeking the following documents related to the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) study (ClinicalTrials.gov number NCT00233324) conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.

(1) All versions of the protocol for the SUPPORT study
(2) All versions of the sample template for the consent/parental permission form for the SUPPORT study

Checked on Friday. This is ready to go tomorrow and we will post on the NICHD Website with links to the NIH website.
We will alter the letter slightly as we will be sending out the complete response rather than a partial response.

Mona

Mona Jaffe Rowe, M.C.P.
Associate Director for Science Policy,
Analysis and Communication
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health, DHHS
Building 31, Rm 2A-18
31 Center Drive
Bethesda, MD 20892-2425
Phone: 301.496.1877/Fax: 301.496.0588
Email: rowem@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 05, 2013 3:06 PM
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Preemie studies - heads up

Andrea,

The attached is the cover letter that presumably will be revised to date for Monday. The foia is for

all versions we have a support protocol. I am cc-ing Mona Rowe to be sure I have not misspoken.

Also, there are outstanding foia requests from public citizen for the protocols and consents for the other studies being conducted in the Newborn Research Network. Those are mostly ready to go.

We have reviewed these materials (b)(5)
(b)(5)

And, on behalf of the entire NIH, congratulations on your new position!

Kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 05, 2013 2:37 PM
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: Preemie studies - heads up

(b)(5)

I have list of docs for FOIA that I will send in separate email.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 5, 2013, at 1:48 PM, "Palm, Andrea (HHS/IOS)" <Andrea.Palm@hhs.gov> wrote:

> Thanks Kathy. Do we know what they included re consent? And just so we know, what is going to public citzen as part of the FOIA response? Thanks.
>
> ---
>
> **From:** Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
> **Sent:** Sunday, May 05, 2013 12:54 PM
> **To:** Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
> **Cc:** Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
> **Subject:** Preemie studies - heads up
>
> http://jama.jamanetwork.com/article.aspx?articleid=1684963
>
> Wanted to make sure you were aware that Canadian study analogous to SUPPORT was published online in JAMA this morning. (b)(5)
> (b)(5)

(b)(5)

Also, on semi related note, information on our newborn research network studies will be sent to public citizen in response to FOIA tomorrow (we are at the deadline) and we will subsequently post on our Webpages.

Too much going on!

Let me know if you have questions.

Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

From: Hudson, Kathy (NIH/OD) [E]
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]
Subject: RE: Preemie studies - heads up
Date: Sunday, May 05, 2013 3:06:08 PM
Attachments: Partial Release Letter.pdf

Andrea,

The attached is the cover letter that presumably will be revised to date for Monday. The foia is for all versions we have a support protocol. I am cc-ing Mona Rowe to be sure I have not misspoken.

Also, there are outstanding foia requests from public citizen for the protocols and consents for the other studies being conducted in the Newborn Research Network. Those are mostly ready to go.

We have reviewed these materials (b)(5)

(b)(5)

And, on behalf of the entire NIH, congratulations on your new position!

Kathy

From: Hudson, Kathy (NIH/OD) [E]
Sent: Sunday, May 05, 2013 2:37 PM
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: Preemie studies - heads up

(b)(5)

I have list of docs for FOIA that I will send in separate email.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 5, 2013, at 1:48 PM, "Palm, Andrea (HHS/IOS)" <Andrea.Palm@hhs.gov> wrote:

> Thanks Kathy. Do we know what they included re consent? And just so we know, what is going to public citzen as part of the FOIA response? Thanks.
>
> ---
>
> **From:** Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]

Sent: Sunday, May 05, 2013 12:54 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Preemie studies - heads up

http://jama.jamanetwork.com/article.aspx?articleid=1684963

Wanted to make sure you were aware that Canadian study analogous to SUPPORT was published online in JAMA this morning. (b)(5)
(b)(5)

(b)(5)

Also, on semi related note, information on our newborn research network studies will be sent to public citizen in response to FOIA tomorrow (we are at the deadline) and we will subsequently post on our Webpages.

Too much going on!

Let me know if you have questions.

Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

National Institutes of Health
Eunice Kennedy Shriver National
Institute of Child Health and
Human Development
Bethesda, Maryland 20892

April 30, 2013

Michael A. Carome, M.D.
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

FOIA Case No. 41203

Dear Dr. Carome:

This is a partial response to your two April 8, 2013 Freedom of Information Act (FOIA) requests addressed to Earl Blansfield. You requested a copy of all institutional review board-approved versions of the consent/parental permission forms for the study site's enrolled subjects in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized (SUPPORT) Study (ClinicalTrials.gov #NCT00233324), conducted by the NICHD Neonatal Research Network. In addition, you requested a copy of all versions of the protocol and all versions of the sample template for the consent/parental permission form for the Surfactant, Positive Pressure, and Pulse Oximetry Randomized (SUPPORT) Study (ClinicalTrials.gov #NCT00233324).

We searched the files of the NICHD Pregnancy and Perinatology Branch. So far, that search produced 259 pages responsive to your request. This partial release includes seven versions of the SUPPORT study protocol. The most recent version of the protocol is included in this response and is also available online at http://www.nih.gov/icd/od/foia/index.htm#foialibrary. We are still in the process collecting and clearing documents related to IRB approved consent/parental permission forms and the sample template for the consent/parental permission form.

In certain circumstances provisions of the FOIA and Department of Health and Human Services FOIA Regulations allow us to recover part of the cost of responding to your request. Because the cost is below the $25 minimum, there is no charge for the enclosed materials.

Sincerely,

Earl H. Blansfield
Freedom of Information Coordinator
National Institute of Child Health and
Human Development
31 Center Drive, Rm. 2A32, MSC 2425
Bethesda, MD 20892

Enclosures: 7 Protocols – 259 pages

From: Palm, Andrea (HHS/IOS)
To: Hudson, Kathy (NIH/OD) [E]
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: Preemie studies - heads up
Date: Sunday, May 05, 2013 2:37:52 PM

Thanks.

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Sunday, May 05, 2013 02:36 PM
To: Palm, Andrea (HHS/IOS)
Cc: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Re: Preemie studies - heads up

(b)(5)
I have list of docs for FOIA that I will send in separate email.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On May 5, 2013, at 1:48 PM, "Palm, Andrea (HHS/IOS)" <Andrea.Palm@hhs.gov> wrote:

Thanks Kathy. Do we know what they included re consent? And just so we know, what is going to public citzen as part of the FOIA response? Thanks.

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Sunday, May 05, 2013 12:54 PM
To: Koh, Howard (HHS/OASH); Menikoff, Jerry (HHS/OASH); Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject: Preemie studies - heads up

http://jama.jamanetwork.com/article.aspx?articleid=1684963

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(b)(5)

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Too much going on!

Let me know if you have questions.

Kathy

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

From:	Guttmacher, Alan (NIH/NICHD) [E]
To:	Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc:	Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject:	RE: Support study -
Date:	Saturday, May 04, 2013 3:49:30 PM

And it really is wonderful using this as a teachable moment, as the expanded letter does.

Best, Alan

From: Menikoff, Jerry (HHS/OASH)
Sent: Saturday, May 04, 2013 3:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Thanks again, Kathy, to you and Alan and your colleagues for the collegial manner in which we reached this point. And we will welcome the similar discussions that you mentioned that will be needed as we move forward.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Saturday, May 04, 2013 03:27 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Thanks for taking time to chat on a spring Saturday afternoon. Here are the edits we discussed.

Have a great week end everyone.

Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie

(NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

From:	Menikoff, Jerry (HHS/OASH)
To:	Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc:	Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject:	Re: Support study -
Date:	Saturday, May 04, 2013 3:36:07 PM

Thanks again, Kathy, to you and Alan and your colleagues for the collegial manner in which we reached this point. And we will welcome the similar discussions that you mentioned that will be needed as we move forward.

Best,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Saturday, May 04, 2013 03:27 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
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Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
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For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

From:	Hudson, Kathy (NIH/OD) [E]
To:	Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc:	Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject:	RE: Support study -
Date:	Saturday, May 04, 2013 3:27:53 PM
Attachments:	SUPPORT revisited 5-3-2013c nih.docx

Thanks for taking time to chat on a spring Saturday afternoon. Here are the edits we discussed.

Have a great week end everyone.

Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From:	Menikoff, Jerry (HHS/OASH)
To:	Higgins, Rosemary (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc:	Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject:	Re: Support study -
Date:	Saturday, May 04, 2013 6:49:55 AM

And if you are referring to the status of a final version of this letter, after it has been sent to UAB: I would expect that, consistent with usual policies, this would get posted on an OHRP web site, a couple weeks after the letter was sent out.

Jerry

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 03, 2013 06:17 PM
To: Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Is this in the public domain?

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 04:53 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

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Best,
Jerry

From:	Menikoff, Jerry (HHS/OASH)
To:	Higgins, Rosemary (NIH/NICHD) [E]; Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc:	Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject:	Re: Support study -
Date:	Friday, May 03, 2013 6:48:44 PM

This a draft of a letter that OHRP might consider releasing. It is merely a revised version of the letter that we have been discussing. It certainly has not been made public, and should not be shared outside of this group.

Jerry

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, May 03, 2013 06:17 PM
To: Menikoff, Jerry (HHS/OASH); Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -

Is this in the public domain?

Rosemary D. Higgins
Program Scientist for the NICHD Neonatal Research Network

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 04:53 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -

Kathy,

For your weekend enjoyment, here is the revised version of the SUPPORT letter.

Best,
Jerry

Carr, Sarah (NIH/OD) [E]

From: Menikoff, Jerry (HHS/OASH)
Sent: Friday, May 03, 2013 4:54 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: Support study -
Attachments: SUPPORT revisited 5-3-2013c.docx

Kathy,

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Best,
Jerry

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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(b)(5)

of the Freedom of Information and Privacy Act

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(b)(5)

of the Freedom of Information and Privacy Act

From: Menikoff, Jerry (HHS/OASH)
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: Support study -
Date: Wednesday, May 01, 2013 10:41:45 PM

Kathy,

This is great to hear! I will look forward to closing up that last micron on our end.

Thanks,
Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 10:17 PM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Support study -

Thanks so much Jerry. This marks a real turning point. I have left your edits intact and added our single suggested edit.

(b)(5)

Best,
Kathy

From: Menikoff, Jerry (HHS/OASH)
Sent: Wednesday, May 01, 2013 6:46 PM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: RE: NIH support summary - nih response

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Sent: Wednesday, May 01, 2013 12:11 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
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Subject:	Support study -
Date:	Wednesday, May 01, 2013 10:17:44 PM
Attachments:	Follow-up SUPPORT letter 5-1-2013 1009pm.docx

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Subject: RE: NIH support summary

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Subject: RE: NIH support summary - nih response
Attachments: Follow-up SUPPORT letter 5-1-2013.docx

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Sent: Wednesday, May 01, 2013 6:20 AM
To: Hudson, Kathy (NIH/OD) [E]; Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Subject: Re: NIH support summary - nih response

Kathy,

Thank you for all of your work on this. On our end, we share your commitment to produce a mutually acceptable resolution to this, and will be getting back to you with that in mind.

Jerry

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Wednesday, May 01, 2013 12:10 AM
To: Menikoff, Jerry (HHS/OASH); Koh, Howard (HHS/OASH); Jones, Wanda K. (DHHS/OS/OASH); Bumpus, Kirby (HHS/OASH)
Cc: Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
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Subject: NIH support summary - nih response
Attachments: Follow-up SUPPORT letter 2NICHD edits klh.docx

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Best,
Jerry

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

(b)(5)

We regret any confusion regarding this matter.

From:	Devaney, Stephanie (NIH/OD) [E]
To:	Patterson, Amy (NIH/OD) [E]
Cc:	Carr, Sarah (NIH/OD) [E]; Fennington, Kelly (NIH/OD) [E]
Subject:	Fw: Fwd: NIH two pager SUPPORT 042413 11PM
Date:	Thursday, April 25, 2013 9:14:17 AM
Attachments:	NIH two pager SUPPORT 042413 11PM fsc.docx ATT00001.htm

Hi Amy, see some edits from FC on the 3 pager. Do you have time to consult on it this morning? I need to get it back around to folks this morning. This was a wonderful write up.

Thank you!

Steph

From: Hudson, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 08:20 AM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: Fwd: NIH two pager SUPPORT 042413 11PM

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

From: "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>
Date: April 25, 2013, 5:48:05 AM EDT
To: "Hudson, Kathy (NIH/OD) [E]" <Kathy.Hudson@nih.gov>
Subject: RE: NIH two pager SUPPORT 042413 11PM

Saw a few things here that might need refinement....

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 11:41 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject: NIH two pager SUPPORT 042413 11PM

Caya,
You asked for a two pager on the support study by 1 pm tomorrow. Please accept our slightly longer (3.15 pages) that has not undergone extensive review here but please know that the nih team is all standing firmly together about our views on this. (b)(5)

(b)(5)

kathy

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

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(b)(5)

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From:	Lewis, Caya (HHS/IOS)
To:	Hudson, Kathy (NIH/OD) [E]
Cc:	Palm, Andrea (HHS/IOS); Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]
Subject:	RE: NIH two pager SUPPORT 042413 11PM
Date:	Thursday, April 25, 2013 12:48:30 PM
Attachments:	NEJM--Editorial.pdf Cochrane Review of use of oxygen 2009.pdf NEJM--Support study results.pdf
Importance:	High

Kathy,

(b)(5)

(b)(5)

From: Hudson, Kathy (NIH/OD) [E] [mailto:Kathy.Hudson@nih.gov]
Sent: Thursday, April 25, 2013 12:19 AM
To: Lewis, Caya (HHS/IOS)
Cc: Palm, Andrea (HHS/IOS); Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject: Re: NIH two pager SUPPORT 042413 11PM

It would be great if you could send us the specific studies ohrp is citing. Our folks are familiar with every study in this area. They live and breath this work and will be able to tell you how the ohrp cited studies fit into the overall portrait of studies on preemies.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
NIH
301 496 1455
kathy.hudson@nih.gov

On Apr 25, 2013, at 12:04 AM, "Lewis, Caya (HHS/IOS)" <Caya.Lewis@hhs.gov> wrote:

Thanks so much for the quick turn around.

(b)(5)

Thanks again,

Caya

From: Hudson, Kathy (NIH/OD) [E] [Kathy.Hudson@nih.gov]
Sent: Wednesday, April 24, 2013 11:40 PM
To: Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject: NIH two pager SUPPORT 042413 11PM

Caya,

(b)(5)

Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants (Review)

Askie LM, Henderson-Smart DJ, Ko H

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Lisa M Askie[1], David J Henderson-Smart[2], Henry Ko[3]

[1]NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia. [2]NSW Centre for Perinatal Health Services Research, Queen Elizabeth II Research Institute, Sydney, Australia. [3]Centre for Clinical Effectiveness, Southern Health, Clayton, Australia

Contact address: Lisa M Askie, NHMRC Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, NSW, 2050, Australia. laskie@ctc.usyd.edu.au.

Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2009.
Review content assessed as up-to-date: 14 August 2008.

Citation: Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD001077. DOI: 10.1002/14651858.CD001077.pub2.

ABSTRACT

Background

While the use of supplemental oxygen has a long history in neonatal care, resulting in both significant health care benefits and harms, uncertainty remains as to the most appropriate range to target blood oxygen levels in preterm and low birth weight infants. Potential benefits of higher oxygen targeting may include more stable sleep patterns and improved long-term growth and development. However, there may be significant deleterious pulmonary effects and health service use implications resulting from such a policy.

Objectives

To determine whether targeting ambient oxygen concentration to achieve a lower vs. higher blood oxygen range, or administering restricted vs. liberal supplemental oxygen, effects mortality, retinopathy of prematurity, lung function, growth or development in preterm or low birth weight infants.

Search strategy

The standard search strategy of the Neonatal Review Group was used. An additional literature search was conducted of the MEDLINE and CINAHL databases in order to locate any trials in addition to those provided by the Cochrane Controlled Trials Register (CENTRAL/CCTR). Search updated to week two July 2008.

Selection criteria

All trials in preterm or low birth weight infants utilising random or quasi-random patient allocation in which ambient oxygen concentrations were targeted to achieve a lower vs. higher blood oxygen range, or restricted vs. liberal oxygen was administered were eligible for inclusion.

Data collection and analysis

The methodological quality of the eligible trials was assessed independently by each review author for the degree of selection, performance, attrition and detection bias. Data were extracted and reviewed independently by the each author. Data analysis was conducted according to the standards of the Cochrane Neonatal Review Group.

Main results

In the meta-analysis of the five trials included in this review, the restriction of oxygen significantly reduced the incidence and severity of retinopathy of prematurity without unduly increasing death rates The one prospective, multicenter, double-blind, randomized trial investigating lower vs. higher blood oxygen levels from 32 weeks postmenstrual age showed no significant differences in the rates of ROP, mortality or growth and development between the two groups. However, this study did show increased rates of chronic lung disease and home oxygen use.

Authors' conclusions

The results of this systematic review confirm that (the now historical) policy of unrestricted, unmonitored oxygen therapy has potential harms without clear benefits. However, the question of what is the optimal target range for maintaining blood oxygen levels in preterm/LBW infants was not answered by the data available for inclusion in this review.

PLAIN LANGUAGE SUMMARY

Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Restricting oxygen supplementation significantly reduces the rate and severity of vision problems (retinopathy) in premature and low birth weight babies. Babies born either prematurely (before 37 weeks) or with a low birth weight often have breathing problems and need extra oxygen. Oxygen supplementation has provided many benefits for these babies but can cause damage to the eyes (retinopathy) and lungs. The review of trials found that unrestricted oxygen supplementation has these potential adverse effects without any clear benefits. Restricted oxygen significantly reduces these risks. More research is needed to find the best level of oxygen supplementation.

BACKGROUND

The administration of supplemental oxygen has a long history in neonatal care (Wilson 1942). The use of oxygen in preterm and low birth weight infants suffering respiratory insufficiency has resulted in significant health care benefits, such as reduced mortality and spastic diplegia (Avery 1960; McDonald 1963), but has also been associated with significant deleterious effects such as retinopathy of prematurity and lung toxicity (Duc 1992).

Improvements in technology in the past few decades have led to both the increased survival of preterm and low birth weight infants and an ability to measure their oxygen levels more accurately. Despite the exceedingly common use of supplemental oxygen in this population of infants, there is little consensus as to the optimal mode of administration and appropriate levels of oxygen for maximising short or long-term growth and development, while minimising harmful effects (Poets 1998; McIntosh 2001).

Uncertainty remains as to the most appropriate range to target blood oxygen levels in preterm and low birth weight infants. Usher (Usher 1973) examined the effect of targeting a lower vs. higher range of PaO_2 on death, the need for mechanical ventilation and other clinical outcomes and concluded there was no benefit in targeting a higher range, and there may in fact be deleterious respiratory effects (Coates 1982). A cohort study by Tin et al (Tin 2001) also suggested an increase in adverse respiratory outcomes and a significant increase in the incidence of ROP occurred when higher oxygen ranges were targeted in preterm infants. However, Phelps and Rosenbaum (Phelps 1984) demonstrated significantly more severe retinopathy in kittens recovering from hyperoxic-induced disease when allowed to recover in lower levels of ambient oxygen, suggesting that targeting higher blood oxygen levels may be beneficial to visual outcomes. The STOP-ROP trial (STOP-ROP 2000) found that higher oxygen targeting did not significantly decrease the incidence of pre-threshold ROP progression, but did cause an exacerbation of adverse pulmonary events. The results of this trial are included in a separate Cochrane review entitled: "Supplemental oxygen for the treatment of pre-threshold retinopathy of prematurity" (Lloyd 2003). The effects of either policy of oxygen administration on long-term growth and development in preterm or low birth weight infants remains uncertain.

Two related Cochrane reviews have summarised the findings on

gradual vs. abrupt (Askie 2001a) and early vs. late discontinuation of oxygen therapy (Askie 2001b) in preterm or low birth weight infants.

OBJECTIVES

To determine whether targeting ambient oxygen concentration to achieve a lower vs. higher blood oxygen range, or administering restricted vs. liberal supplemental oxygen effects mortality, retinopathy of prematurity, lung function, growth or development in preterm or low birth weight infants.

A priori sub-group analyses:

- Method of oxygen monitoring. Infants born at different gestational age and birth weight subgroups: as there are differing baseline risks of the outcome measures in these subgroups. Time of discontinuation: early vs. late discontinuation as this is hypothesized to influence outcome measures (Gunn 1980). Method of discontinuation: gradual vs. abrupt discontinuation as this is hypothesized to influence outcome measures (Chan-Ling 1995)

METHODS

Criteria for considering studies for this review

Types of studies

Trials utilising random or quasi-random patient allocation were eligible for inclusion.

Types of participants

Preterm (< 37 weeks gestation) or low birth weight (< 2500 g) infants receiving supplemental oxygen.

Types of interventions

Restricted vs. liberal administration of supplemental oxygen; or targeting a lower vs. higher range of blood oxygen levels.

Types of outcome measures

- Retinopathy of prematurity (ROP) - any, severe (stage 3 or greater)
- Mortality - any, early neonatal period (< 1 week postnatal age), later neonatal period (≥ 3 weeks postnatal age)
- ROP (severe) or death (any)
- Apnea of prematurity
- Chronic lung disease/bronchopulmonary dysplasia
- Growth - neonatal period and long-term
- Neurodevelopment - long-term
- Visual function - long-term

Outcome data with attrition rates greater than 20% were not included in analyses.

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. This includes searches of the Cochrane Controlled Trials Register (CENTRAL/CCTR, The Cochrane Library, Issue 2, 2008), the Oxford Database of Perinatal trials, MEDLINE, previous reviews including cross references, abstracts, conferences and symposia proceedings, expert informants, journal hand searching mainly in the English language.

An additional literature search, using OVID software, was conducted of the MEDLINE (1996 - June, Week 2, 2008), Maternity and Infant Care (1971 - June 2008), and CINAHL (1982 - June 2008) databases in order to locate any trials in addition to those provided by the Cochrane Controlled Trials Register (CENTRAL/CCTR, The Cochrane Library, Issue 2, 2008). The search strategy involved various combinations of the following keywords, using the search fields of abstract, MeSH subject heading, exploded subject heading, floating subject heading, publication type, registry number word, subject heading word, text word, and title: oxygen, preterm, premature, neonate, newborn, infant, oxygen saturation, hypoxia, retinopathy of prematurity, retrolental fibroplasia, low birth weight, very low birth weight, extremely low birth weight, randomized controlled trial, controlled clinical trial, clinical trial, random allocation, placebo.

Data collection and analysis

The standard methods of the Cochrane Collaboration and its Neonatal Review Group were used to select trials, assess quality and extract and synthesise data. For each trial, each author independently assessed the methodological quality and extracted the data from the report. Results were compared and differences resolved as required. Level of agreement between the two authors was greater than 90% in all cases. Eligible trials were assessed for the degree of selection, performance, attrition and detection bias. Additional information was requested from authors to clarify methodology or results as necessary.

Meta-analyses were carried out with use of relative risk (RR) and risk difference (RD). When appropriate, number needed to treat (1/RD) was calculated. The fixed effects "assumption free" model was used. Evaluation of heterogeneity, subgroup and sensitivity analyses were undertaken as appropriate.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The systematic review located six trials that addressed the question of targeting oxygen administration in preterm/LBW infants. Fourteen other studies were excluded from the analysis as they either did not address this particular question or did not involve random allocation of one of the interventions under review.

Participants:

The enrolment period for five included studies was between 1951 - 1969 (referred to as "pre-1990" trials or studies hereon in) and one (Askie 2003) included study was conducted between 1996 - 2000 (referred to as "post-1990" trials or studies hereon in). The five pre-1990 studies were done during an early era of neonatal care, with therapies and practices quite different from modern "intensive" care. These studies included only small numbers of survivors with birth weights under 1000 g, the infants who carry the greatest mortality and morbidity burden today. There was a wide range of birth weights among trial participants, from less than 1000 to 2500 g. The largest pre-1990 era trial (Kinsey 1956) only enrolled infants who survived beyond 48 hours, while the other four trials randomized infants on admission to the neonatal nursery anywhere from two hrs (Usher 1973) to > 48 hours (Kinsey 1956). Infants from these five trials have been categorised as belonging to the early neonatal period (< 1 week postnatal age), which was defined as treatments starting at < 1 week of age. The only post-1990 trial (Askie 2003) enrolled infants < 30 weeks gestation who remained dependent on supplemental oxygen at 32 weeks postmenstrual age; therefore, infants in this trial were at least three weeks postnatal age at randomization. Infants in this trial have been defined in this review as belonging to the later neonatal period ($\geq$ 3 weeks postnatal age). The five pre-1990 trials used birth weight as inclusion criteria, with the most recent trial using gestational and postmenstrual age as inclusion criteria. Three trials also selected infants for inclusion based on a diagnosis of respiratory distress syndrome (Usher 1973) or hypoxia/acidemia (Sinclair 1968) or continued dependence on supplemental oxygen more than three weeks after birth (Askie 2003).

Intervention:

Three trials (Askie 2003; Usher 1973; Sinclair 1968) administered oxygen based on actual arterial, saturation or capillary blood oxygen levels. The other three trials were conducted in an era before accurate blood oxygen monitoring in infants was possible. As such, these trials could only test the effects of cruder measures of oxygenation, such as ambient oxygen concentration, and even these in only general terms, labelled "liberal" and "restricted" oxygen administration in this review. For the included studies, due to the variation in measurement methods, restricted oxygen ranged from values of Fn SpO_2 91-94% (Askie 2003), either 0.4 or 0.5 maximum FiO_2 (Kinsey 1956; Lanman 1954; Patz 1954), or PaO_2<45mmHg (PcapO2<35mmHg) (Usher 1973) or maximum O_2 of 35% (in a headbox, PaO_2 50-120mmHg) (Sinclair 1968). Liberal O_2 ranged from values of Fn SpO_2 95-98% (Askie 2003), O_2 levels at 50% (Kinsey 1956), 60-70% (Patz 1954), or 100% (in a headbox; PaO_2 50-120mmHg) (Sinclair 1968), FiO_2 69% (Lanman 1954), or minimum O_2 40% (PaO_2 80-120mmHg or $PcapO_2$ 50-60mmHg) (Usher 1973).

Five of the included trials started the intervention in the early neonatal period (< 1 week postnatal age), but continued it for a wide range of time; from one day to seven weeks. Of these, four studies randomized infants from birth (defined as $\leq$ 48 hours after birth) (Lanman 1954; Patz 1954; Sinclair 1968; Usher 1973), while one study did not randomize infants until > 48 hours after birth (Kinsey 1956). One trial started the intervention in the later neonatal period (from 32 weeks postmenstrual age) (Askie 2003), and continued for a median of 17.5 days (IQR 7.0 to 41.0 days) for lower oxygen targeting and a median of 40.0 days (IQR 20.5 to 73.0 days) for the higher oxygen targeting group. When oxygen weaning was indicated, it was done so gradually in two trials, abruptly in one trial, and the method not specified in the remaining three trials.

Outcomes:

Outcome measures were assessed at time periods ranging from two days to 12 months. Only Askie 2003 reported the longer term (12 months corrected age) effects of the interventions on growth, neurodevelopment, lung function, or chronic lung disease. Coates 1982 reported some long-term outcomes on infants from Usher's 1973 study (Usher 1973). Unfortunately, he was only able to obtain outcome data for 23% of survivors, and in keeping with our *a priori* specification of only including outcome measures with 80% or greater ascertainment, these data are not included in the review. Only one study (Askie 2003) reporting eye outcome data used the International Classification of Retinopathy of Prematurity grading system (ROP Committee 1984). This was assessed by routine ophthalmic examinations at two-week intervals from enrolment until the resolution of retinopathy.

The only other study to report eye outcome data used the retrolental fibroplasia (RLF) classifications (Reese 1953). Vascular RLF grade 1, vascular RLF grade 2, and cicatricial RLF / RLF grade 3 correspond approximately with retinopathy of prematurity (ROP) stage 3, ROP stage 4, and ROP stage 5 / blindness respectively. These inferred classifications were gathered from references to RLF/ROP cross-classification from the International Classification of Retinopathy of Prematurity system (ROP Committee 1984; ROP Committee 1987; Garner 1985; Hindle 1986; Hindle 1990; Sira 1988; Szewcyk 1953). Ascertainment of RLF in the five trials from 1951 - 1969 was by direct ophthalmoscope, visualising the posterior pole only. The only findings that could be identified using this method were dilation and tortuosity of the retinal vessels ("plus disease", using the 1984 and 1987 classifications, as above). The more common findings in the anterior pole that can today be

identified with indirect ophthalmoscopy were unable to be identified. Hence, even the least severe eye outcomes reported in this review equate with what today would be described as "threshold" ROP.

The largest trial (Askie 2003, n = 358) only enrolled infants who survived and were oxygen dependent beyond three weeks postnatal age. The second largest trial (Kinsey 1956, n = 212) only enrolled infants who survived beyond 48 hours. Unfortunately, the third largest trial (Patz 1954, n = unknown, but greater than 120) did not report any mortality data and these data are not retrievable (Duc 1992).

Risk of bias in included studies

All included trials used either quasi-random or random patient allocation, had at least one clinically meaningful outcome, and were thus included in the analyses. The overall methodological quality of the included trials was fair. Askie 2003 stratified the randomization with the use of a dynamic balancing method to ensure a balance of treatment group assignment within each stratum defined according to hospital, singleton or multiple birth, and gestational age.

Three of the trials had adequate allocation concealment: Askie 2003 and Kinsey 1956 used central telephone randomization, and Sinclair 1968 used a method of sealed envelopes. Allocation concealment is unclear in the other three trials. Patz 1954 used quasi-random patient allocation, while the remaining five trials were truly randomized. Askie 2003 was the only trial to employ masking with families, clinicians and outcome assessors in this trial unaware of treatment allocation. Askie 2003 and Kinsey 1956 were the only two trials to report power calculations *a priori*. Five of the included studies had adequate short-term outcome measure ascertainment. The Patz 1954 trial did not report deaths or losses to follow-up, but it is assumed that outcome data were reported only on survivors and assessed by six months age.

Effects of interventions

RESTRICTED VS. LIBERAL OXYGEN THERAPY (ALL PRETERM/LBW INFANTS) IN EARLY NEONATAL PERIOD (Comparison 1):

In this meta-analysis, restricted compared with liberal oxygen administration when started during the early neonatal period did not have any statistically significant effect on the incidence of death. It should be noted that there were a range of times for enrolment in this early period from two hrs (Usher 1973) to > 48 hrs (Kinsey 1956). However, restricted oxygen administration did significantly reduce the incidence of all forms of retrolental fibroplasia (RLF) in survivors. Cicatricial RLF (any grade) was significantly reduced in surviving infants who were exposed to a restricted oxygen regime (summary RR 0.26, 95% CI 0.11-0.58). There was also a significant reduction in the precursor, vascular RLF (any stage), in surviving infants exposed to restricted oxygen (summary RR 0.34, 95% CI CI 0.25-0.46).

During the early neonatal period, neither restricted compared with liberal oxygen administration nor lower vs. higher blood oxygen levels (where blood oxygen was directly measured) had significant independent effects on death rates, either in all preterm/LBW infants or in a sub-group of infants with birth weights < 1250 g. However, restricted compared with liberal oxygen administration did significantly reduce a combined measure of adverse outcome, death or RLF (vascular, any stage) (summary RR 0.59, 95% CI 0.48-0.72). Thus, one would need to treat only three infants with restricted oxygen to prevent one infant from having the adverse outcome of death or RLF (NNT = 1/RD = 1/0.310 = 3.2). Restricted compared with liberal oxygen administration also reduced the more severe measure of adverse outcome, death or RLF (cicatricial, any grade) (summary RR 0.77, 95% CI 0.56-1.07) for the trial where the intervention was used in the early neonatal period, although this result was not statistically significant.

No other outcome measures specified *a priori* as clinically meaningful were reported in enough detail or with satisfactory follow-up rates to be included in the analysis (chronic lung disease; long-term growth, development, lung or visual function).

SUBGROUP ANALYSIS FOR THE EARLY NEONATAL PERIOD (Comparisons 2-4):

Only one of the *a priori* stated subgroup analyses was possible with the available data for the early neonatal period.

Subgroup analysis of lower vs. higher blood oxygen levels in the early neonatal period showed that for infants with BW < 1250 g weeks gestational age, there was no significant difference in the incidence of death. However, it should be noted that this trial (Usher 1973) only enrolled 45 infants.The only reported effect of restricted vs. liberal oxygen saturation targeting on infants with birth weight less than 1000g was a non-significant decrease in RLF (cicatricial, severe) in the Patz 1954 trial. The analysis was based on very small numbers, with uneven denominators in each group. This may reflect a difference in the number of survivors in the two groups resulting from deaths which were not accounted for by Patz 1954. This result should thus be interpreted with caution as the small numbers in this subgroup (as reflected in the wide confidence intervals) and non-reported deaths make any meaningful interpretation of these data difficult.

It was not possible to undertake any of the other *a priori* specified subgroup analyses such as time or method of oxygen weaning, or a comprehensive analysis of the method of oxygen monitoring due to insufficient data.

LOWER VS. HIGHER BLOOD OXYGEN LEVELS (ALL PRETERM/LBW INFANTS) IN THE LATER NEONATAL

PERIOD (Comparison 5):

Only one study (Askie 2003), with 358 infants, contributed to the results in the later neonatal period. There was no significant difference in the incidence of death between lower or higher oxygen saturation targeting when started in the later neonatal period. There were no statistically significant differences in the incidence of ROP (any stage) in survivors, the incidence of ROP > Stage 2 nor ROP Stage 4 or 5 or blindness between the infants receiving lower or higher oxygen saturation targeting. There were no statistically significant differences between intervention strategies for the combined outcomes of death or ROP > Stage 2, nor with death or ROP Stage 4 or 5 or blindness.

Some outcome measures specified *a priori* as clinically meaningful were reported. There was no statistically significant difference in the incidence of major developmental abnormality at 12 months corrected age between lower or higher oxygen saturation targeting. In relation to lung function, there was a significant reduction on the dependence of supplemental oxygen at 36 weeks of postmenstrual age with using a lower oxygen saturation target (RR 0.71, 95% CI 0.59-0.87). There was no statistically significant difference between interventions for the incidence of use of postnatal corticosteroids and diuretics for chronic lung disease with the use of either a lower or higher oxygen saturation targeting.

Some outcomes were either not reported at all or not reported in enough detail or with satisfactory follow-up rates to be included in the analysis (long-term lung or visual function).

SUBGROUP ANALYSIS FOR THE LATER NEONATAL PERIOD (Comparison 6):

Only one of the *a priori* stated subgroup analysis could be undertaken with the available data for the later neonatal period.

Comparison of lower vs. higher oxygen saturation targeting when started in the later neonatal period in infants < 28 weeks gestational age revealed no statistically significant difference in the incidence of death, ROP Stage 3 or 4, nor in the incidence of blindness.

Evaluation of heterogeneity:

No statistical heterogeneity was demonstrated in any of the outcome measures analysed that included more than one trial.

There was considerable clinical heterogeneity amongst the six trials included in this review. All included trials contained a wide range of birth weights, followed infants for a relatively wide ranging period (and all but one in the short-term only), used different definitions of outcome measures (five trials used RLF and one trial used ROP eye outcome definitions), and implemented the interventions in either an early or later neonatal period. There was a very wide range of exposure to the interventions under review (1 day to >10 weeks). Moreover, there were three distinct intervention comparisons included in the review (hence the division of comparisons into restricted vs. liberal oxygen administration in the early neonatal period, lower vs. higher blood oxygen levels in the early neonatal period, and lower vs. higher blood oxygen levels in the later neonatal period). The Kinsey 1956, Lanman 1954 and Patz 1954 trials were conducted in an early (pre-1990) era of neonatal care where methods of oxygen monitoring and administration were crude in comparison to today's techniques and thus only restricted vs. liberal oxygen administration could be compared in these trials. The Usher 1973 and Sinclair 1968 trials used more modern techniques (including umbilical artery catheterization, arterialised capillary sampling, micromethods for blood gases and acid-base), so comparison of lower vs. higher blood oxygen levels were possible with these data. The Askie 2003 trial used pulse oximeters whose algorithm assessed functional oxygen saturation, and thus comparisons of lower vs. higher blood oxygen level via oxygen saturation targets were possible with data from these trials.

Sensitivity analyses:

The results of the meta-analyses were tested for robustness with regard to study quality. We had stated *a priori* that trials containing outcome measures with greater than 20% attrition would not be included in the analysis. In one trial, Patz 1954, it was unclear whether outcome ascertainment was complete as attrition due to losses to follow-up and deaths were not reported. This, plus the fact that it was the only trial using a quasi-random method of patient allocation, led us to test the results without the inclusion of this trial.

There were two outcome measures for the early neonatal period analysis that included data from the Patz 1954 trial. The outcomes to which the Patz trial contributed were RLF (vascular, any stage) and RLF (cicatricial, severe grades). The results for neither of these outcome measures were significantly affected by the exclusion of the Patz trial. Hence, the results of these meta-analyses were not sensitive to the effect of study quality.

DISCUSSION

The answer to the question of what is the optimal therapeutic range of blood oxygen level for preterm/LBW infants to maximise benefits, while minimising harms, remains uncertain.

To date only two randomized trials (Askie 2003; Usher 1973) have attempted to address this question directly. Sinclair 1968 assessed the effects of lower vs. higher blood oxygen levels and other co-interventions in a group of hypoxic, acidaemic low birth weight infants. The related, but now historic, question of restricted vs. liberal oxygen administration was addressed by three randomized trials (Kinsey 1956; Lanman 1954; Patz 1954) in an era before accurate and/or continuous monitoring of infant blood oxygen levels was possible. Both interventions were included in this review, which addresses the general question of the effect of oxygen dose on outcomes for preterm/LBW infants.

In this analysis, restricting oxygen exposure in the early neonatal period significantly reduced the incidence and severity of RLF

without unduly increasing death rates. The results of the largest trial contributing to these outcomes (Kinsey 1956) have often been misinterpreted, with the resulting extrapolation of aggressive restriction of oxygen from birth leading to a substantial increase in mortality rates among preterm/LBW infants in the years following its publication (Cross 1973). This trial did not enrol infants until at least 48 hours of age. It should also be noted that the second largest trial, Patz 1954, did not report any mortality data and this information is not retrievable (Duc 1992). Unfortunately, the confidence intervals around the point estimate for this outcome are quite wide (RR 1.20, 95% CI 0.80-1.80), and the addition of the Patz 1954 mortality data would have been helpful in resolving this issue. It is possible that the difference in RLF rates seen in survivors may be influenced by the trend toward excess deaths caused by the restricted oxygen policy.

Since the publication of these earlier era trials, other authors have attempted to further investigate the association between RLF/ROP and blood oxygen levels. A large, prospective, non-randomized study (Kinsey 1977) involving a detailed survey across five collaborating centres in the USA was undertaken between 1969 and 1972. No definitive relationship between blood oxygen levels and the occurrence of RLF could be established. It should be noted that this analysis was undertaken using the limited information available from intermittent blood gas sampling. The study did find an association between susceptibility to RLF and decreasing birth weight and increasing time in oxygen. However, no guidelines for the optimal range of blood oxygen level were suggested by this study.

Two trials (Sinclair 1968; Usher 1973) that addressed the question of low vs. higher blood oxygen levels in the early neonatal period (< 1 week postnatal age) found no significant effect on death in the early neonatal period, but did not report (in sufficient detail to warrant inclusion) the effect of this intervention on eye or other outcomes. The effects of either of these oxygen administration policies on other clinically meaningful outcomes, including chronic lung disease, long-term growth, neurodevelopment, lung or visual function were not reported.

No further trials were undertaken until a prospective, multicenter, double-blind, randomized, controlled trial (Askie 2003) involving eight collaborating centres in Australia was conducted between 1996 and 2000. There were no significant differences in the rates of ROP at any stage between the lower and higher oxygen saturation target groups in the later neonatal period ($\geq$ 3 weeks postnatal age). There were no significant differences between the groups in mortality rates either. However, this study noted that there was a disadvantage to using higher oxygen saturation targeting because of the increase in the proportion of infants needing oxygen therapy for longer, as well as supplemental oxygen after discharge. Again, this study made no recommendations for an optimal blood oxygen level, but suggested that targeting higher blood oxygen levels may increase the burden of health services for these infants. This trial enrolled oxygen-dependent infants at 32 weeks postmenstrual age who were at least 3 weeks of age. There is therefore a need to evaluate this therapy when commenced soon after birth as this may alter the rates of ROP or death. A number of trials currently underway are examining this (BOOST NZ (NZ); BOOSTII (Australia); BOOSTII (UK); COT (Canada); SUPPORT (USA)).

All studies included in this review measured eye outcomes. Unlike the pre-1990 studies, the Askie 2003 trial also reported the effect of interventions on growth and development. However, these outcomes were not measured beyond 12 months corrected age and thus studies with longer term outcomes will need to be conducted. Since 2001, several observational studies (Tin 2001; Anderson 2004; Sun 2002; Chow 2003) have been published that have suggested short-term ophthalmic and respiratory outcomes might be significantly improved by a policy of lower oxygen range targeting without causing increases in mortality or long-term morbidity. However, these non-randomized studies lack adequate statistical power to exclude possible small, but important, increases in death and disability that could have major implications if a policy of lower oxygen targeting was implemented worldwide. Currently, there are five ongoing randomized trials being conducted to assess the effects of lower vs. higher oxygen saturation levels in extremely preterm infants from birth. The individual patient data from these trials will be combined in a prospective meta-analysis to help resolve this remaining question.

The role of careful, continuous monitoring of oxygen levels on the incidence of retinopathy of prematurity has also been investigated by several authors since the publication of the earlier studies included in this review. Bancalari and co-workers (Bancalari 1987a; Bancalari 1987b; Flynn 1987) conducted the only large randomized trial of continuous transcutaneous PO_2 monitoring to date. This study showed no significant difference in the incidence or severity of ROP, mortality or chronic lung disease in the continuously monitored infants compared with those who received standard (intermittent) monitoring of PO_2 levels. The utility of pulse oximetry monitoring in preventing adverse neonatal outcomes remains largely untested. The value of pulse oximetry in reducing major hypoxic events during anaesthesia among 152 children undergoing surgery has been assessed in one study (Cote 1988). Another trial (Watkin 1999) compared near infrared spectroscopy and pulse oximetry in the detection of hypoxaemia in neonates with pauses in nasal airflow. Roemer and colleagues (Roemer 2005) examined the diagnostic power of pulse oximetry, other blood oxygen measures and acid-base measurements for hypoxia in term fetuses. However, randomized controlled trial evidence for the effectiveness of pulse oximetry monitoring in the early neonatal period is still unavailable.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review confirm that (the now historical) policy of unrestricted, unmonitored oxygen therapy has potential harms without clear benefits. However, the question of what is the optimal target range for maintaining blood oxygen levels in preterm/LBW infants in the modern clinical setting from birth or soon thereafter was not answered by the data available for inclusion in this review.

Implications for research

As the question of what is the optimal target range for maintaining blood oxygen levels remains unclear, further research should be undertaken to resolve this important clinical question. An ongoing international collaboration is attempting to address this issue. The BOOSTII trials (BOOST NZ (NZ); BOOSTII (Australia); BOOSTII (UK); COT (Canada); SUPPORT (USA)) are all assessing the effects of higher oxygen levels on infants 27 weeks or less gestational age in terms of both short and long-term outcomes. Results from these trials will be combined in a prospective meta-analysis (known as the NeOProM Collaboration) and will be incorporated into this systematic review as they become available. The STOP-ROP trial (STOP-ROP 2000) assessed the effect of higher oxygen levels on the progression of pre-threshold ROP. The results of this trial are included in a separate Cochrane review entitled: "Supplemental oxygen for the treatment of pre-threshold retinopathy of prematurity" (Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO). It should be noted that this trial did not address the effect of oxygen levels administered in the early neonatal period either as infants were 35.6 weeks postmenstrual age at enrolment into this trial.

ACKNOWLEDGEMENTS

None.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Askie 2003

Methods	Randomization was stratified with the use of a dynamic balancing method to ensure a balance of treatment-group assignment within each stratum defined according to hospital, singleton or multiple birth, and gestational age. Central telephone randomization ensured adequate allocation concealment. The intervention group (standard oxygen) received oxygen to achieve Fn SpO_2 91-94%, while the control group (high oxygen) received oxygen to achieve Fn SpO_2 95-98%. Masking of all interventions was achieved by using oximeters designed to display levels either 2% higher or lower than what it really was, thereby giving readings between 93-96%. Caregivers were not aware of the offset level (double-blinding). There were no losses in follow-up. There were detailed power calculations.
Participants	358 infants < 30wks gestation who remained dependent on supplemental oxygen at 32 wks of postmenstrual age. The mean birth weight for standard saturation group was 918g and for high saturation group 916g. Infants were followed and measured at 12 months corrected age.
Interventions	Experimental group (standard oxygen): received oxygen to achieve Fn SpO_2 91-94%. Intervention treatment applied at 32wks postmenstrual age and maintained for the duration of the supplemental oxygen therapy. Control group (high oxygen): received oxygen to achieve Fn SpO_2 95-98%. Intervention treatment applied at 32 wks postmenstrual age and maintained for the duration of the supplemental-oxygen therapy.
Outcomes	Worst retinopathy of prematurity (< stage 3) Worst retinopathy of prematurity (stage 3 or 4) Ablative retinal surgery for severe retinopathy of prematurity Death (after randomization) Growth measures: - weight - length - head circumference Major developmental abnormality Dependence on supplemental oxygen at 36 wks of postmenstrual age Home-based oxygen therapy & duration of oxygen therapy after randomization Postmenstrual age at cessation of oxygen therapy Duration of assisted ventilation after randomization Postnatal corticosteroids Diuretics for chronic lung disease Length of stay after randomization Postmenstrual age at discharge from hospital Postmenstrual age at time of fully oral feeding Infant rehospitalized Number of health service visits per infant

Askie 2003 (*Continued*)

	Scores on psychological measures -Edinburgh postnatal depression scale (mother) -infant temperature scale -toddler temperment scale -parenting stress index, short form -impact-on-family scale
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomization was stratified with the use of a dynamic balancing method.
Allocation concealment?	Yes	Central telephone randomization.
Blinding? All outcomes	Yes	Oxygen saturation levels were adjusted to display a value 2% higher than the actual saturation in infants in the standard O2 group or 2% lower than the actual saturation in infants in the high-saturation group.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up for outcome data.
Free of selective reporting?	Yes	All outcomes were reported.

Kinsey 1956

Methods	Central telephone randomization ensured adequate allocation concealment. The ratio of experimental group : control group was 2:1 in first 3 months of enrolment. Following that, 574 infants were consecutively allocated to the experimental group and had no concurrent controls. These infants are not included in this review. The number of infants excluded before randomization is not known. Randomization was stratified by birth weight categories and institution. The intervention was not blinded and the blinding of outcome assessments is unclear. The follow-up rate for outcome measures was 97%. There were detailed power calculations.
Participants	212 infants with BW <1500g who survived to 48 hours. Enrolment commenced in July 1953. The mean BW in the two groups was 1242g (restricted)and 1234g (liberal) respectively. Infants were followed until 2.5 months of age.
Interventions	Experimental group (restricted oxygen): received oxygen only if clinical condition indicated and maximum FiO_2 permitted was 0.5. Control group (liberal oxygen): received supplemental oxygen in excess of 50% for a minimum of 28 days and were then weaned over 3 days.

Kinsey 1956 (*Continued*)

Outcomes	Vascular RLF (any stage) in survivors Vascular RLF (severe stages) in survivors Cicatricial RLF (any grade) in survivors Cicatricial RLF (severe grades) in survivors Mortality (48 hours-40 days) Of the 144 infants assigned to the restricted oxygen group, 36 died before 40 days and 4 were lost to follow-up. There were 15 deaths and no losses to follow-up among the 68 infants allocated to the liberal oxygen group.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Block and stratified randomization.
Allocation concealment?	Yes	Central telephone randomization.
Blinding? All outcomes	No	Blinding not stated.
Incomplete outcome data addressed? All outcomes	Yes	Follow-up was 97%. Reasons were given for loss to follow-up (e.g. death)
Free of selective reporting?	Yes	There were 21 tables and 8 appendices tables of results and measured data reporting various analyses of the outcome data and breakdown of the characteristics of the populations from all the participating centres.

Lanman 1954

Methods	Infants were randomized by random numbers, method unspecified, and thus allocation concealment is unclear. There was no blinding of the intervention and it is unknown if outcome assessments were done blinded to treatment allocation. There was only one loss to follow-up of the 86 infants enrolled. Power calculations were inadequate with the completion of the study being determine by a date specified one year in advance.
Participants	86 infants with BW 1000-1850g admitted within 12 hours of birth. Infants were followed until 3 months age.
Interventions	Experimental group (restricted oxygen): only received oxygen when cyanosed, at a maximum FiO_2 of 0.5. The mean FiO_2 received by this group was 0.38. Control group (liberal oxygen): received supplemental oxygen for a minimum of 2 weeks or until reaching 1500g, and were then weaned abruptly. The mean FiO_2 received by this group was 0.69.

Lanman 1954 (*Continued*)

Outcomes	Vascular RLF (any stage) in survivors Cicatricial RLF (any grade) in survivors Mortality (12 hours-3 months)	
Notes		

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random numbers, but method was not specified.
Allocation concealment?	Unclear	Allocation was in order of admission by random numbers but method was not specified. Allocated to one of 4 groups: high oxygen, high oxygen + estrogen given orally, low oxygen, & low oxygen + estrogen given orally.
Blinding? All outcomes	No	For restricted oxygen intervention, oxygen was given only when infants were cyanosed, so blinding would not have been easily done.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up, and infants who were lost lost to follow-up were accounted for.
Free of selective reporting?	Yes	All participants and outcomes were reported, even those that were lost to follow-up were reported.

Patz 1954

Methods	Quasi-random treatment allocation, based on alternate admission basis. Allocation concealment was thus inadequate. There was no blinding of the intervention and it is unclear whether outcome assessments were blinded to treatment allocation. Attrition due to deaths or losses to follow-up are not reported, so it is unclear whether there was complete outcome measure ascertainment. No power calculations were reported.
Participants	An unknown number of very low birthweight infants (</= 1500g) were enrolled from Jan 1951 to May 1953. 120 infants survived and had eye outcome assessments completed by 6 months age and were included in the analysis.
Interventions	Experimental group (restricted oxygen): infants received oxygen only for clinical indications, and to a maximum FiO_2 of 0.4. The range of duration of oxygen in this group was 1 day - 2 weeks. Once weaning was indicated, it proceeded over 1-3 days.

Patz 1954 (*Continued*)

	Control group (liberal oxygen): infants were placed in supplemental oxygen of 60-70% for 4-7 weeks, then weaned over one week.
Outcomes	Vascular RLF (any stage) in survivors Cicatricial RLF (severe grades) in survivors Cicatricial RLF (severe grades), BW <1000g, in survivors There are no data available, either published or unpublished, on mortality rates. The number of infants allocated to each group was not reported, hence outcome data can only be expressed in relation to the surviving infants presenting for follow-up assessment.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Quasi-random allocation based on alternate admission basis.
Allocation concealment?	No	Quasi-random allocation based on alternate admission basis.
Blinding? All outcomes	No	Blinding not stated. Also, the experimental and control interventions were applied for different lengths of time, so treatment differences would have been obvious.
Incomplete outcome data addressed? All outcomes	Unclear	The focus of results seemed to be on qualitative histological data. The quantitative results seemed to report on all outcomes.

Sinclair 1968

Methods	Randomized to one of 4 treatment groups, using sealed envelopes and thus allocation concealment was adequate. There was no blinding of treatment intervention, and it is unclear whether there was blinding of outcome assessments. No power calculations were reported. Short-term follow up was complete.
Participants	20 infants with BW 1000-2500g less than 24 hours age who were hypoxic and acidemic were included.
Interventions	Infants were randomized to one of four treatment groups including combinations of the following treatments: restricted vs. liberal ambient oxygen, rapid vs. slow alkali infusion, assisted vs. spontaneous ventilation. There was random allocation of the other two treatments within the two oxygen therapy groups, hence the data from this trial were included in the review. Experimental group (restricted oxygen): supplemental oxygen, to a maximum of 35%, to keep PaO_2 50-120 mmHg. If PaO_2 fell below 40 mmHg or infant became bradycardic, could give unlimited oxygen and would be considered as a treatment failure.

Sinclair 1968 (*Continued*)

	Control group (liberal oxygen): received 100% headbox oxygen for first 2 hours, then aimed to maintain PaO_2 at 50-120 mmHg using any FiO_2 needed.
Outcomes	Mortality (any) Physiological measures including: - acid-base balance - PaO_2 levels - percentage right-left shunt - serum electrolytes, blood urea nitrogen, serum lactate - urinary net acid excretion - plasma bicarbonate - "apparent" bicarbonate space Long-term neurological assessments reported as "in progress" in the paper were never completed (personal communication J. Sinclair, July 1998).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Sealed envelopes & stratified
Allocation concealment?	Yes	Random allocation to 1 of 4 treatment groups, using sealed envelopes; stratified by severity of A (severe vs. moderate).
Blinding? All outcomes	No	Blinding not stated.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up (but not specified). Short-term follow-up was complete.
Free of selective reporting?	Yes	There were 14 tables and 15 figures of results and analysed data reporting various analyses of the outcome data. It seemed all outcomes were reported.

Usher 1973

Methods	Infants were randomized by a stratified random sampling technique. Allocation concealment is unclear. There was no blinding of the intervention. One author was unblinded to the treatment allocation, but is unclear whether this author was involved in outcome assessments. No power calculations were reported. Early outcome data were reported completely. However, long-term outcome data included only 15% of the enrolled infants and thus have not been included in this review.
Participants	150 infants with a diagnosis of respiratory distress syndrome or BW <1000g were eligible for inclusion. The numbers excluded prior to randomization are not reported.
Interventions	Experimental group (low PaO_2): infants received oxygen only if their PaO_2 fell below 40 mmHg or $PcapO_2$ fell below 35 mmHg. Sufficient oxygen was used to maintain these tensions. Control group (high PaO_2): infants were kept in a minimum of 40% oxygen for 72 hours. Aim was to maintain PaO_2 80-120 mmHg or $PcapO_2$ 50-60 mmHg. Mechanical ventilation was not available to either group.
Outcomes	Mortality (any) Mortality (respiratory) Descriptive results of respiratory failure measures were reported (such as retractions, grunting, respiratory pattern and rate, chest Xray changes).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Stratified random sampling technique.
Allocation concealment?	Unclear	Unclear
Blinding? All outcomes	No	Blinding not stated.
Incomplete outcome data addressed? All outcomes	Yes	There was complete follow-up for early outcomes, but not for late outcomes. Only 15% follow-up at 10yrs (Coates).
Free of selective reporting?	Yes	There were 10 tables and 16 figures of results and analysed data reporting various analyses of the outcome data. It seemed that all outcomes were reported.

Characteristics of excluded studies *[ordered by study ID]*

Bard 1996	Infants were not randomly assigned to target two different arterial blood oxygen saturations (90% and 95%). Infants acted as their own controls. This was not a random or quasi-random trial and was thus excluded from the review.
Cunningham 1995	This non-randomized, retrospective study assessed the effects of variability of oxygen levels, as measured by transcutaneous oxygen monitoring, on the incidence of retinopathy of prematurity. Patient allocation was not randomized, and thus the study was excluded from the review.
Deulofeut 2007	This was a non-randomized study of infants from January 2000 to December 2004, where there was a change from SpO_2 92-100% to SpO_2 85-93% from January 2003. Since allocation of treatment was non-randomized, this study was excluded from the review.
Engleson 1958	This non-randomized trial addressed a different question from that under review. It examined the effects of keeping preterm infants at oxygen concentrations below that of room air, and was thus not included in the review.
Fitzgerald 1998	Infants in this study were randomized to receive either air/usual supplementary oxygen (to maintain SpO_2 >93%) or increased supplementary oxygen (to maintain SpO_2 >97%) only for one night whilst the sleep study was done. Included trials randomized infants to an ongoing policy of higher / lower SpO_2. Infants also already had CLD at the start of the study (which was one of this study's population inclusion criteria).
Gaynon 1997	The study was a retrospective analysis of different target ranges of oxygen saturation on the incidence of ROP. There was no random allocation of patients to different treatment groups, thus the trial was excluded from the review.
Kitchen 1978	This study was a randomized trial of a "package" of intensive care, including intravenous glucose, umbilical arterial catheterisation, bicarbonate infusion, and high PaO_2 levels, vs. the standard neonatal care regimen of the late 1960s. The trial was excluded from the review because the entire "package" of interventions, rather than the separate elements within it, was the randomized intervention. Thus, other interventions that could affect clinical outcomes were unbalanced between oxygen exposure groups.
Lundstrom 1995	This randomized trial addressed a different question from that under review. It compared the use of atmospheric air vs. 80% oxygen for preterm infants during initial stabilization in the delivery room, and was thus excluded from the review.
Mendicini 1971	This study was a randomized trial of a "package" of intensive care, including intravenous glucose, bicarbonate infusion, and high PaO_2 levels, vs. the standard neonatal care regimen of the late 1960s. The trial was excluded from the review because the entire "package" of interventions, rather than the separate elements within it, was the randomized intervention. Thus, other interventions that could affect clinical outcomes were unbalanced between oxygen exposure groups.
Schulze 1995	This was a non-randomized, crossover trial comparing the effects of two different oxygen saturation target ranges on cardiac output, oxygen extraction, and oxygen consumption in mechanically ventilated, low birth weight infants. As treatment allocation was not random or quasi-random, the trial was excluded from the review.

(*Continued*)

STOP-ROP 2000	This trial included preterm/LBW infants with pre-threshold ROP. The intervention tested was supplemental oxygen for the treatment of pre-threshold ROP, not a preventative strategy. The results of this trial will be included in a separate Cochrane review entitled: "Supplemental oxygen in the treatment of pre-threshold retinopathy of prematurity" (Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO).
Wallace 2007	This was a non-randomized retrospective cohort study of infants. Eligible infants born between October 1, 2002, and July 31, 2003, were given SpO2 98-100%. Eligible infants born between January 1, 2004, and April 30, 2005, were given SpO_2 90-96%. Since allocation of treatment was non-randomized, this study was excluded from the review.
Weintraub 1956	The planned scheme of quasi-random, alternate allocation was not adhered to, resulting in the possibility of substantial selection bias, and the study was thus excluded from the review.
Wright 2006	This was a non-randomized prospective observational study of infants from 3 centres where there was a change in SpO_2 from >90%, 89-94% or 90-95% to 83-93% for all centres. Eligible infants born after the transition year were given the lower SpO2 treatment. Since allocation of treatment was non-randomized, this study was excluded from the review.

Characteristics of ongoing studies *[ordered by study ID]*

BOOST NZ (NZ)

Trial name or title	Benefits of oxygen saturation targeting trial (NZ)
Methods	Infants are randomized centrally by telephone, using a computerized interactive voice response system. Randomization is stratified by site, sex, gestation and inborn and outborn. Computer-generated randomization lists are prepared by an independent statistician and not accessible to staff involved in the daily care of infants. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO2 by +/-3% points. Staff will (a) target SpO_2 88-92% and (b) aim to maximize time spent with SpO_2 between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO_2. Outside 85-95%, study oximeters read actual SpO_2. 320 infants will be enrolled. This data will be analysed with the data from the Australian BOOST-II trial. A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO_2 85-89%) vs higher (Fn SpO_2 91-95%) O_2 targeting
Outcomes	Survival and major disability at 2 years corrected age, other secondary outcomes
Starting date	2006
Contact information	Professor Brian Darlow; Email: brian.darlow@chmeds.ac.nz

BOOST NZ (NZ) (*Continued*)

Notes	

BOOSTII (Australia)

Trial name or title	Benefits of oxygen saturation targeting trial 2 (Australia)
Methods	Infants are randomized centrally by telephone, using a computerized interactive voice response system. Randomization is stratified by site, sex, gestation and inborn and outborn. Computer-generated randomization lists are prepared by an independent statistician and not accessible to staff involved in the daily care of infants. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO2 by +/-3% points. Staff will (a) target SpO_2 88-92% and (b) aim to maximize time spent with SpO_2 between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO_2. Outside 85-95%, study oximeters read actual SpO_2. A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO_2 85-89%) vs higher (Fn SpO_2 91-95%) O_2 targeting
Outcomes	Death or major disability at 2 years corrected age, other secondary outcomes
Starting date	2006
Contact information	Alpana Ghadge; Tel: +61 2 9562 5000; Fax: +61 2 9562 5094
Notes	

BOOSTII (UK)

Trial name or title	Benefits of oxygen saturation targeting trial 2 (UK)
Methods	Infants are randomized centrally by a secure website at the National Perinatal Epidemiology Unit (NPEU) in Oxford. A computer-generated program that used minimization will be used to ensure balanced allocation to the two arms of the trials in each recruiting unit from a knowledge of weight, gestation and sex at birth. The NPEU is write the randomization program and hold the code. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO2 by +/-3% points. Staff will (a) target SpO_2 88-92% and (b) aim to maximize time spent with SpO_2 between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO_2. Outside 85-95%, study oximeters read actual SpO_2. A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%. Data analysis will be intention to treat.

BOOSTII (UK) (*Continued*)

Participants	Infants <28 weeks' gestation at birth and <12 hours old (24 hours old if the baby is outborn)
Interventions	Lower (Fn SpO_2 85-89%) vs higher (Fn SpO_2 91-95%) O_2 targeting
Outcomes	Death or serious neurosensory disability at 2 years corrected age, other secondary outcomes
Starting date	2007
Contact information	Professor Peter Brocklehurst; Email: peter.brocklehurst@npeu.ox.ac.uk
Notes	

COT (Canada)

Trial name or title	Canadian oxygen trial
Methods	Infants are randomized centrally by telephone. Randomization is stratified by gestational age (23-25 and 26-27 weeks) and by study centre. Alocation will incorporate variable block sizes. The concealed study allocation will be determined, in advance, using a computer-based random number generator. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO2 by +/-3% points. Staff will (a) target SpO_2 88-92% and (b) aim to maximize time spent with SpO_2 between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO_2. Outside 85-95%, study oximeters read actual SpO_2. A sample size of 1200 infants has 80% power (2p=0.05) to detect an absolute 8% increase or decrease in the composite outcome of death or major disability at 2 years. This would mean one less infant who died or was disabled for every 12 infants managed in the optimal range. This would have similar power to detect a reduction in severe ROP from 10% to 7.8% and in CLD from 40% to 32%.
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO_2 85-89%) vs higher (Fn SpO_2 91-95%) O_2 targeting
Outcomes	Death or major disability (cognition, neuromotor function, vision, hearing) at 2 years corrected age, other secondary outcomes
Starting date	October 2006
Contact information	Dr Barbara Schmidt; Email: schmidt@mcmaster.ca
Notes	

SUPPORT (USA)

Trial name or title	The surfactant positive airway pressure and pulse oximetry trial in extremely low birth weight infants

SUPPORT (USA) (*Continued*)

Methods	This is a prospective, randomized, factorial 2x2 design multi-centre trial. Randomization will be stratified by gestational age, and will be done utilizing double-sealed envelopes. The individual factors to be tested will be: 1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early (<1 hour) surfactant and mechanical ventilation; 2) A prospective comparison of a lower SpO2 range (85% to 89%) with a higher more conventional SpO2 range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen. The intervention monitored through Masimo Radical SET pulse oximeters are masked by offsetting the assigned SpO2 by +/-3% points. Staff will (a) target SpO_2 88-92% and (b) aim to maximize time spent with SpO_2 between 85-95%. From 85-95%, the offset will be 3% above or below the actual SpO_2. Outside 85-95%, study oximeters read actual SpO_2. Power has been calculated to be 80% for detecting an absolute difference of 10% in the primary and secondary outcomes, with a sample size of 1310.
Participants	Infants <27 weeks' gestation at birth and <24 hours old
Interventions	Lower (Fn SpO_2 85-89%) vs higher (Fn SpO_2 91-95%) O_2 targeting
Outcomes	Death or major disability at 2 years corrected age, survival without BPD at 36 weeks, survival without ROP, other secondary outcomes
Starting date	February 2005
Contact information	Dr Neil Finer; Email: nfiner@ucsd.edu
Notes	

DATA AND ANALYSES

Comparison 1. Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.80, 1.90]
2 Cicatricial RLF (any grade) in survivors	2	221	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.11, 0.58]
3 Vascular RLF (any stage) in survivors	3	341	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.25, 0.46]
4 Vascular RLF (severe stages) in survivors	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.85]
5 Cicatricial RLF (severe grades) in survivors	2	277	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.07, 0.50]
6 Death or vascular (RLF (any stage)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.48, 0.72]
7 Death or cicatricial RLF (any grade)	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.07]
8 Cicatricial RLF (severe grades) in survivors (excluding Patz 1954)	1	157	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.11, 0.93]
9 Vascular RLF (any stage) in survivors (excluding Patz 1954)	2	221	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.26, 0.51]

Comparison 2. Restricted versus liberal oxygen therapy (BW<1000g) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cicatricial RLF (severe grades) in survivors	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.02, 3.79]

Comparison 3. Lower versus higher blood oxygen levels (all preterm/LBW infants) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any)	2	170	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.57, 1.44]

Comparison 4. Lower versus higher blood oxygen levels (BW<1250g) in early neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (any)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.75, 1.58]

Comparison 5. Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.19, 1.64]
2 ROP (any stage) in survivors	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.19]
3 ROP >Stage 2 in survivors	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.77, 2.16]
4 ROP Stage 4 or 5 or blindness in survivors	1	358	Risk Ratio (M-H, Fixed, 95% CI)	5.06 [0.60, 42.85]
5 Death or ROP >Stage 2	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.69, 1.68]
6 Death or ROP Stage 4 or 5 or blindness	1	358	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.43, 2.37]
7 Dependence on supplemental oxygen at 36 weeks of postmenstrual age	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.59, 0.87]
8 Postnatal corticosteroids	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.05]
9 Diuretics for chronic lung disease	1	358	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.68, 1.05]
10 Major developmental abnormality at 12 months corrected age	1	334	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.53]

Comparison 6. Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period

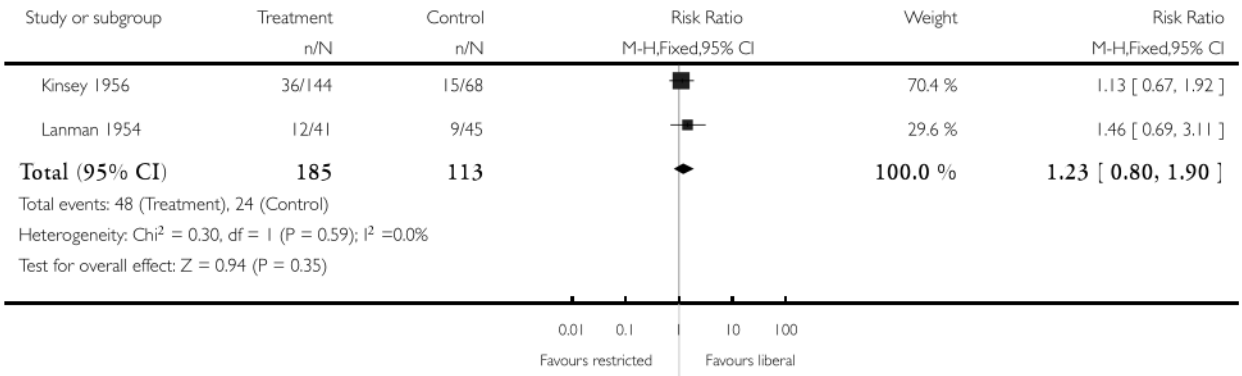
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ROP Stage 3 or 4	1	256	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.85, 2.36]
2 Blindness	1	240	Risk Ratio (M-H, Fixed, 95% CI)	4.14 [0.47, 36.46]

Analysis 1.1. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 1 Death (any).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 1 Death (any)

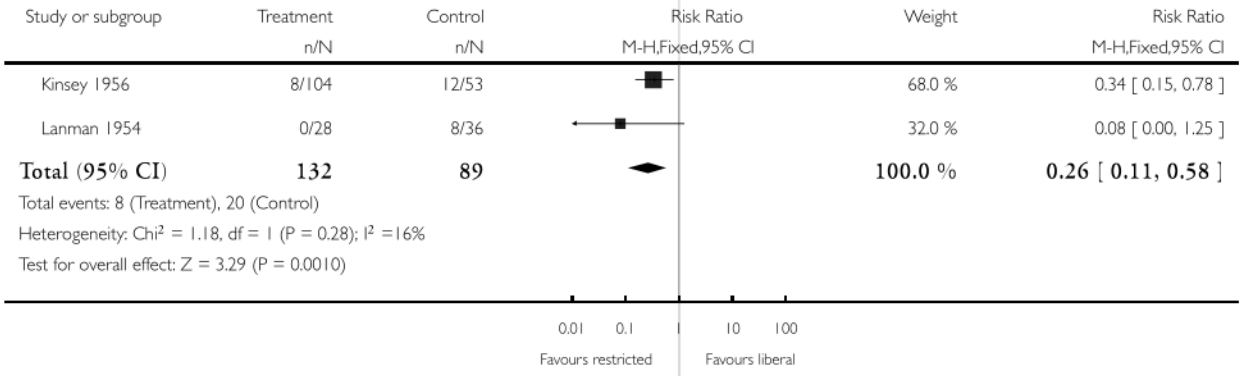


Analysis 1.2. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 2 Cicatricial RLF (any grade) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 2 Cicatricial RLF (any grade) in survivors



Analysis 1.3. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 3 Vascular RLF (any stage) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 3 Vascular RLF (any stage) in survivors

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	34/104	38/53		49.1 %	0.46 [0.33, 0.63]
Lanman 1954	2/28	22/36		18.8 %	0.12 [0.03, 0.46]
Patz 1954	10/60	33/60		32.2 %	0.30 [0.16, 0.56]
Total (95% CI)	**192**	**149**		**100.0 %**	**0.34 [0.25, 0.46]**
Total events: 46 (Treatment), 93 (Control)					
Heterogeneity: Chi^2 = 5.53, df = 2 (P = 0.06); I^2 =64%					
Test for overall effect: Z = 7.00 (P < 0.00001)					

Analysis 1.4. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 4 Vascular RLF (severe stages) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 4 Vascular RLF (severe stages) in survivors

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	9/104	12/53		100.0 %	0.38 [0.17, 0.85]
Total (95% CI)	**104**	**53**		**100.0 %**	**0.38 [0.17, 0.85]**
Total events: 9 (Treatment), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					

Analysis 1.5. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 5 Cicatricial RLF (severe grades) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 5 Cicatricial RLF (severe grades) in survivors

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	5/104	8/53		46.9 %	0.32 [0.11, 0.93]
Patz 1954	1/60	12/60		53.1 %	0.08 [0.01, 0.62]
Total (95% CI)	**164**	**113**		**100.0 %**	**0.19 [0.07, 0.50]**

Total events: 6 (Treatment), 20 (Control)

Heterogeneity: $Chi^2 = 1.51$, df = 1 (P = 0.22); $I^2 = 34\%$

Test for overall effect: Z = 3.39 (P = 0.00070)

Analysis 1.6. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 6 Death or vascular (RLF (any stage).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 6 Death or vascular (RLF (any stage)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	70/144	53/68		70.9 %	0.62 [0.51, 0.77]
Lanman 1954	14/41	31/45		29.1 %	0.50 [0.31, 0.79]
Total (95% CI)	**185**	**113**		**100.0 %**	**0.59 [0.48, 0.72]**

Total events: 84 (Treatment), 84 (Control)

Heterogeneity: $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 5.28 (P < 0.00001)

Analysis 1.7. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 7 Death or cicatricial RLF (any grade).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 7 Death or cicatricial RLF (any grade)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	44/144	27/68		69.4 %	0.77 [0.52, 1.13]
Lanman 1954	12/41	17/45		30.6 %	0.77 [0.42, 1.42]
Total (95% CI)	**185**	**113**		**100.0 %**	**0.77 [0.56, 1.07]**
Total events: 56 (Treatment), 44 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.57 (P = 0.12)					

Analysis 1.8. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 8 Cicatricial RLF (severe grades) in survivors (excluding Patz 1954).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 8 Cicatricial RLF (severe grades) in survivors (excluding Patz 1954)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	5/104	8/53		100.0 %	0.32 [0.11, 0.93]
Total (95% CI)	**104**	**53**		**100.0 %**	**0.32 [0.11, 0.93]**
Total events: 5 (Treatment), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.10 (P = 0.036)					

Analysis 1.9. Comparison 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period, Outcome 9 Vascular RLF (any stage) in survivors (excluding Patz 1954).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 1 Restricted versus liberal oxygen therapy (all preterm/LBW infants) in early neonatal period

Outcome: 9 Vascular RLF (any stage) in survivors (excluding Patz 1954)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kinsey 1956	34/104	38/53		72.3 %	0.46 [0.33, 0.63]
Lanman 1954	2/28	22/36		27.7 %	0.12 [0.03, 0.46]
Total (95% CI)	**132**	**89**		**100.0 %**	**0.36 [0.26, 0.51]**
Total events: 36 (Treatment), 60 (Control)					
Heterogeneity: Chi^2 = 4.60, df = 1 (P = 0.03); I^2 =78%					
Test for overall effect: Z = 5.88 (P < 0.00001)					

Analysis 2.1. Comparison 2 Restricted versus liberal oxygen therapy (BW<1000g) in early neonatal period, Outcome 1 Cicatricial RLF (severe grades) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 2 Restricted versus liberal oxygen therapy (BW<1000g) in early neonatal period

Outcome: 1 Cicatricial RLF (severe grades) in survivors

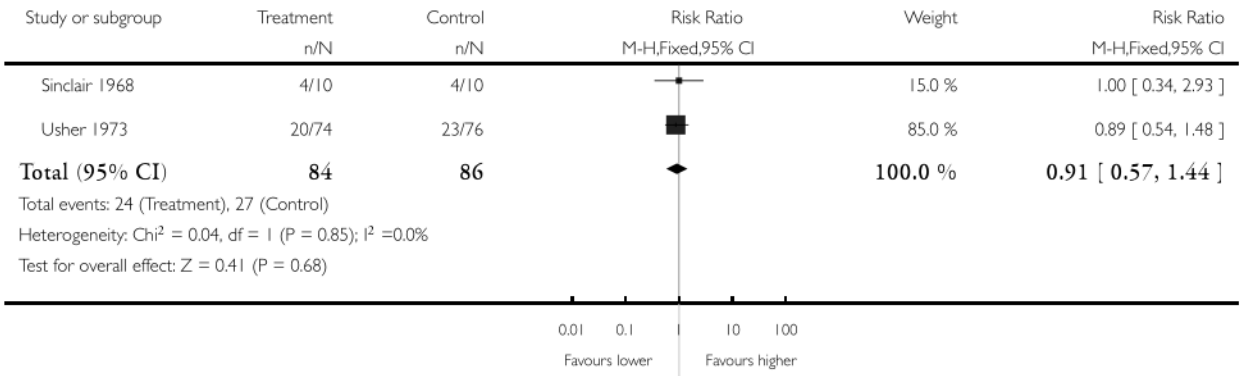
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Patz 1954	0/5	4/12		100.0 %	0.24 [0.02, 3.79]
Total (95% CI)	**5**	**12**		**100.0 %**	**0.24 [0.02, 3.79]**
Total events: 0 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					

Analysis 3.1. Comparison 3 Lower versus higher blood oxygen levels (all preterm/LBW infants) in early neonatal period, Outcome 1 Death (any).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 3 Lower versus higher blood oxygen levels (all preterm/LBW infants) in early neonatal period

Outcome: 1 Death (any)

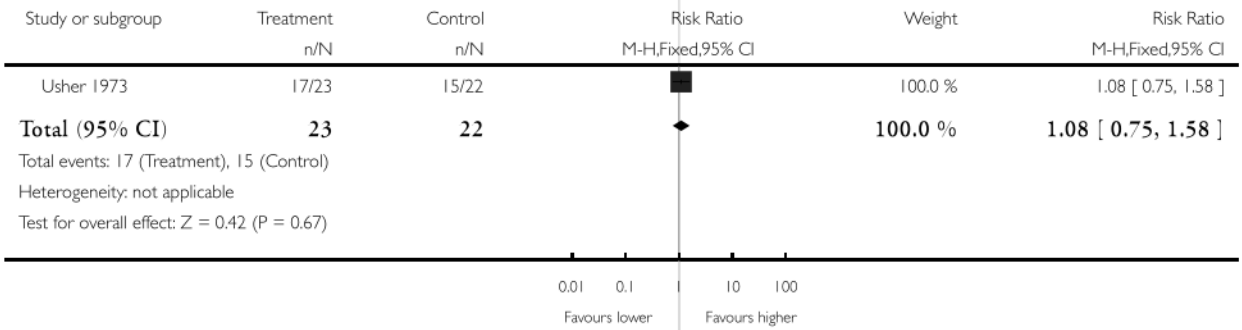


Analysis 4.1. Comparison 4 Lower versus higher blood oxygen levels (BW<1250g) in early neonatal period, Outcome 1 Death (any).

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 4 Lower versus higher blood oxygen levels (BW<1250g) in early neonatal period

Outcome: 1 Death (any)

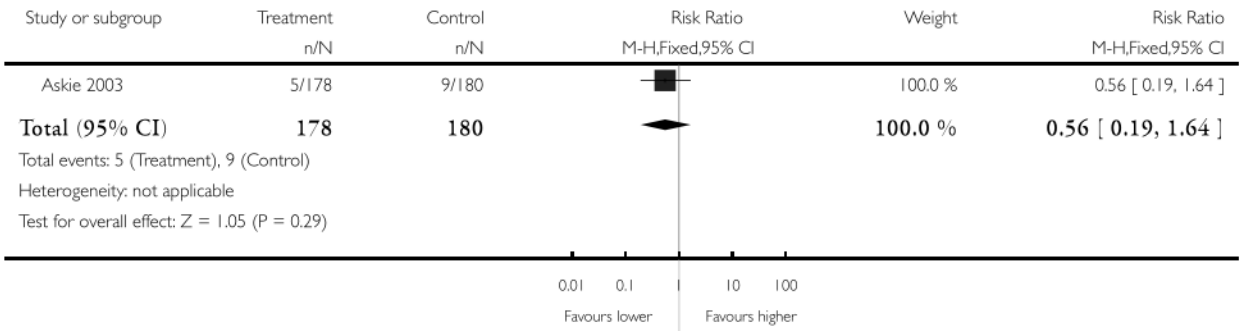


Analysis 5.1. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 1 Death.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 1 Death

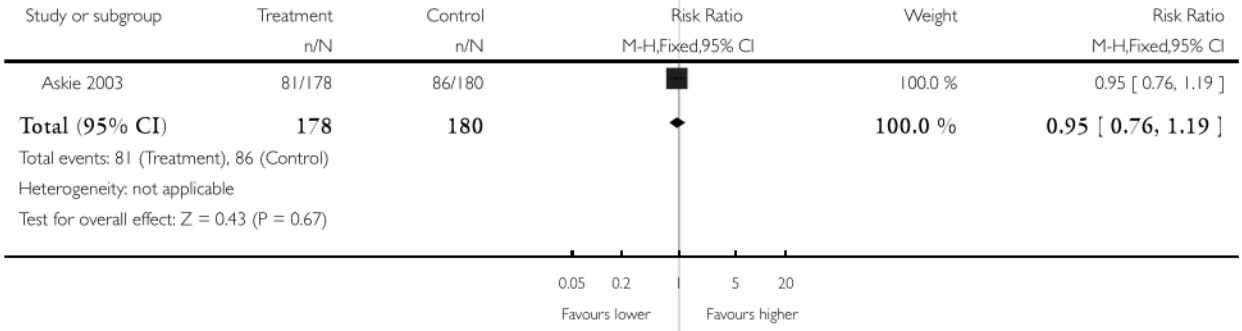


Analysis 5.2. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 2 ROP (any stage) in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 2 ROP (any stage) in survivors



Analysis 5.3. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 3 ROP >Stage 2 in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 3 ROP >Stage 2 in survivors

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askie 2003	28/178	22/180		100.0 %	1.29 [0.77, 2.16]
Total (95% CI)	**178**	**180**		**100.0 %**	**1.29 [0.77, 2.16]**
Total events: 28 (Treatment), 22 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					

Analysis 5.4. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 4 ROP Stage 4 or 5 or blindness in survivors.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 4 ROP Stage 4 or 5 or blindness in survivors

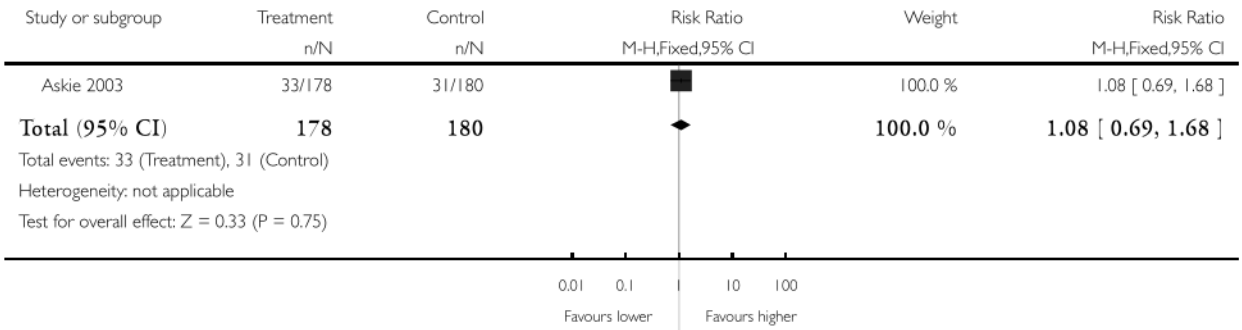
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askie 2003	5/178	1/180		100.0 %	5.06 [0.60, 42.85]
Total (95% CI)	**178**	**180**		**100.0 %**	**5.06 [0.60, 42.85]**
Total events: 5 (Treatment), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					

Analysis 5.5. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 5 Death or ROP >Stage 2.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 5 Death or ROP >Stage 2

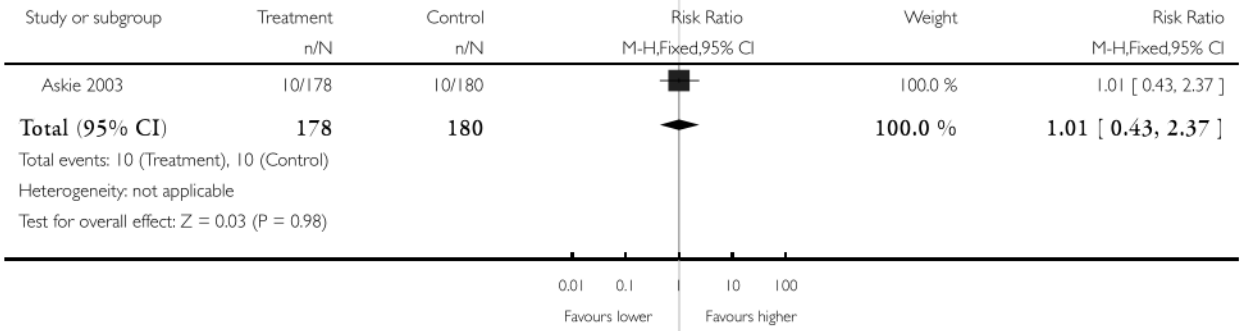


Analysis 5.6. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 6 Death or ROP Stage 4 or 5 or blindness.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 6 Death or ROP Stage 4 or 5 or blindness



Analysis 5.7. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 7 Dependence on supplemental oxygen at 36 weeks of postmenstrual age.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 7 Dependence on supplemental oxygen at 36 weeks of postmenstrual age

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askie 2003	82/178	116/180		100.0 %	0.71 [0.59, 0.87]
Total (95% CI)	**178**	**180**		**100.0 %**	**0.71 [0.59, 0.87]**
Total events: 82 (Treatment), 116 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.42 (P = 0.00063)					

Analysis 5.8. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 8 Postnatal corticosteroids.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 8 Postnatal corticosteroids

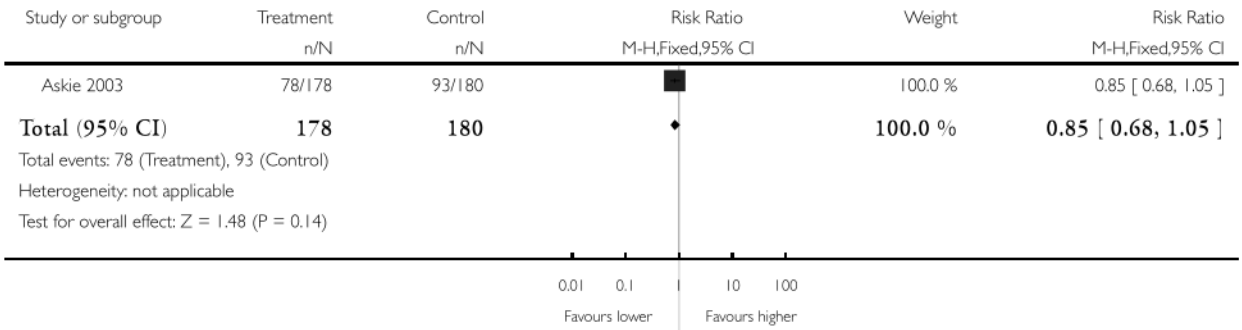
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Askie 2003	89/178	104/180		100.0 %	0.87 [0.71, 1.05]
Total (95% CI)	**178**	**180**		**100.0 %**	**0.87 [0.71, 1.05]**
Total events: 89 (Treatment), 104 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.47 (P = 0.14)					

Analysis 5.9. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 9 Diuretics for chronic lung disease.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 9 Diuretics for chronic lung disease

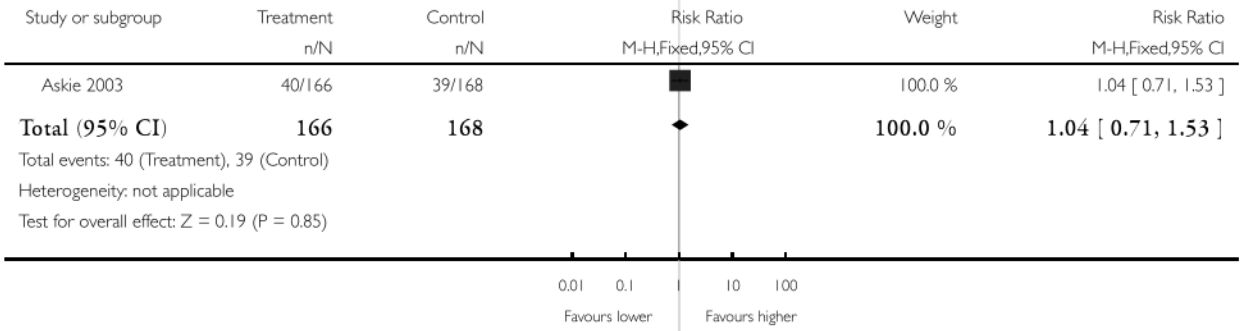


Analysis 5.10. Comparison 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period, Outcome 10 Major developmental abnormality at 12 months corrected age.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 5 Lower versus higher blood oxygen levels (all preterm/LBW infants) in later neonatal period

Outcome: 10 Major developmental abnormality at 12 months corrected age

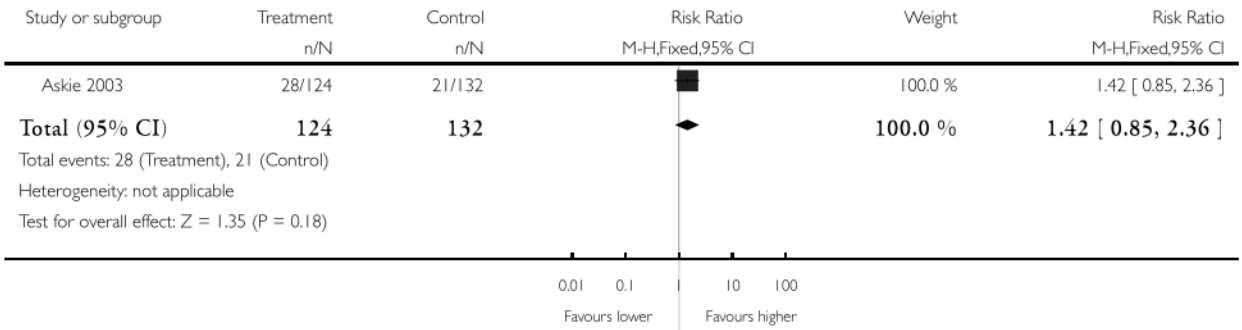


Analysis 6.1. Comparison 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period, Outcome 1 ROP Stage 3 or 4.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period

Outcome: 1 ROP Stage 3 or 4

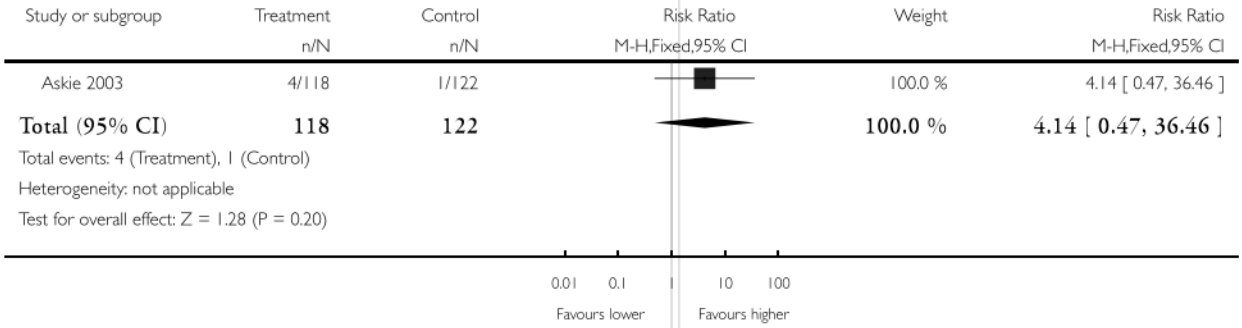


Analysis 6.2. Comparison 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period, Outcome 2 Blindness.

Review: Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants

Comparison: 6 Lower versus higher blood oxygen levels (<28 weeks GA) in later neonatal period

Outcome: 2 Blindness



WHAT'S NEW

Last assessed as up-to-date: 14 August 2008.

13 May 2009	Amended	Minor amendment - References Watkin and Roemer added

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 1999

14 August 2008	New search has been performed	This review updates the existing review "Restricted versus liberal oxygen for preventing morbidity and mortality in preterm or low birth weight infants" published in the Cochrane Database of Systematic Reviews. This update includes an updated literature search, revised Background section including RLF/ROP cross-classification information and references, revised data analysis with a new included study, updated Discussion and conclusion sections, updated information regarding ongoing clinical trials.
14 August 2008	New citation required but conclusions have not changed	Substantive amendment
25 January 2008	Amended	Converted to new review format.
1 October 2003	New search has been performed	This review updates the existing review "Restricted versus liberal oxygen for preventing morbidity and mortality in preterm or low birth weight infants" which was published in the Cochrane Library Issue 2, 2001. The background section has additional references; The STOP-ROP 2000, trial previously listed as ongoing, has now been listed as an excluded trial and will be included in another Cochrane systematic review entitled "Supplemental oxygen in the treatment of pre-threshold retinopathy of prematurity" (Lloyd J, Askie LM, Smith J, Tarnow-Mordi WO); a synopsis and a background section to the abstract have also been added. No new trials were identified as a result of the most recent search, and hence no substantive changes have been made to either the results or conclusions of the review.

CONTRIBUTIONS OF AUTHORS

Askie and Henderson-Smart developed the original protocol for this review, as well as doing the original literature searching, background, data analysis, discussion and conclusions. Askie and Henderson-Smart also contributed to the updated version of the review. Ko updated the review with an updated literature search, background with RLF/ROP cross-classification information and references, data analysis with the new included trial, updated the discussion and conclusions, updated the information on the ongoing clinical trials, and created the GRADE summary of findings tables which will be

included at a later date. Askie and Henderson-Smart reviewed this.

DECLARATIONS OF INTEREST

Askie and Henderson-Smart have conducted and published a randomized, controlled trial of the effect of higher vs. standard oxygen saturation targeting on long-term growth and development of preterm infants.

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, University of Sydney, Australia.
- NSW Centre for Perinatal Health Services Research, University of Sydney, Australia.

External sources

- Department of Public Health and Community Medicine, University of Sydney, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, visual function was to be recorded only in the first year of life, but in the review it was expanded to measure long-term visual function. The outcomes from long-term visual function observations fit well with the original protocol and subsequent review outcome measures of long-term growth and neurodevelopment.

In the current review, results have been split into observations made in the early neonatal period of life and the later neonatal period of life. This differentiation was not stated in the protocol. The splitting of the observations was due to the large time gap between when infants commenced the different oxygen strategies: either early in the neonatal period (< 1 week) and later in the neonatal period ($\geq$ 3 weeks postnatal age).

As stated in the review, some long-term growth and development measures could not be measured due to no data being available for those outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Oxygen Inhalation Therapy [adverse effects]; Infant, Low Birth Weight [*physiology]; Infant, Newborn; Infant, Premature [*physiology]; Infant Mortality; Oxygen [administration & dosage; adverse effects; *blood]; Partial Pressure; Randomized Controlled Trials as Topic; Retinopathy of Prematurity [etiology]

MeSH check words

Humans

EDITORIALS

CPAP and Low Oxygen Saturation for Very Preterm Babies?

Colin J. Morley, M.D.

The survival rate among extremely preterm babies — those born at 24 to 27 weeks of gestation — is about 75%, and there is a high prevalence of neurodevelopmental problems. Reducing the rates of complications and death among these infants is a key research area. Traditionally, extremely preterm babies have been treated with intubation and ventilation soon after birth. However, these interventions may contribute to lung injury. Many infants breathe adequately but not normally at birth, and some can be assisted with the less invasive strategy of nasal continuous positive airway pressure (CPAP) and receive ventilation and surfactant only if this strategy fails.[1,2] Oxygen therapy is very toxic for preterm babies, and maintaining even slightly high arterial levels contributes to retinopathy of prematurity and increases the duration of oxygen treatment.[3] Unfortunately, an oxygen saturation (SpO_2) range that reduces retinopathy of prematurity optimally but does not increase the rates of death or neurodevelopmental problems has not been accurately defined.

The results of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a randomized, 2-by-2 factorial trial in which 1316 babies who were born between 24 weeks 0 days and 27 weeks 6 days of gestation were enrolled, are reported in this issue of the *Journal*.[4,5] In this trial, early treatment with CPAP was compared with immediate intubation followed by surfactant, and a target oxygen saturation range of 85 to 89% was compared with a target range of 91 to 95%.

In one part of the trial,[5] babies were randomly assigned, before birth, to either intubation in the delivery room and surfactant administration within an hour or nasal CPAP started in the delivery room. Babies who were randomly assigned to CPAP could be intubated in the delivery room, for the purpose of resuscitation, or later, if predefined criteria were met. Extubation criteria were also predefined; the criteria for threshold levels of the partial pressure of arterial carbon dioxide ($PaCO_2$), pH, the fraction of inspired oxygen (FiO_2), and SpO_2 were more stringent for the intubation group than for the CPAP group. The rates of the primary outcome of death or bronchopulmonary dysplasia[6] did not differ significantly between the CPAP group and the surfactant group (47.8% and 51.0%, respectively; $P=0.30$). The CPAP group, as compared with the surfactant group, less frequently required intubation in the delivery room (34.4% vs. 93.4%) or postnatal corticosteroids for the treatment of bronchopulmonary dysplasia (7.2% vs. 13.2%) ($P<0.001$ for both comparisons), and required ventilation for an average of 3 days less ($P=0.03$). There were no significant differences between the two groups in the incidences of death or other major outcomes before discharge from the hospital. These results are similar to those of the Continuous Positive Airway Pressure or Intubation at Birth trial (COIN; Australian New Zealand Clinical Trials Registry number, 12606000258550),[2] in which 610 babies who were born at 25 to 28 weeks of gestation were randomly assigned to CPAP or intubation and ventilation at 5 minutes after birth.

Some limitations of the present trial should be noted. Randomization was performed before delivery (i.e., before it was known whether babies would breathe or have respiratory distress); as a result, some of the infants in the CPAP group were intubated immediately after birth and did not receive CPAP. The median duration of ventilation for both groups was 3 to 4 weeks, which was much longer than the 3 to 4 days in the COIN trial,[2] and suggests that the extubation criteria in this trial were more stringent than were those in

the COIN trial. In the COIN trial,[2] pneumothorax occurred in 9.1% of the infants in the CPAP group and in 3.0% of the infants in the ventilation group. In the SUPPORT trial, they occurred in 6.8% of the infants in the CPAP group and in 7.4% of the infants in the ventilation group, a finding that suggests that early CPAP is not associated with pneumothorax.

In the other part of SUPPORT,[4] the babies were randomly assigned to a target range for peripheral oxygen saturation of 85 to 89% or 91 to 95%. Staff members were unaware of the true levels because the oximeters had been altered to read 3% above or 3% below the true reading, so that they displayed a range of 88 to 92% for both ranges. The unmasked trial data showed that the distribution of oxygen saturation levels was within or above the target range in the higher-oxygen-saturation group, but in the lower-oxygen-saturation group, it was about 90 to 95% (i.e., above the target range). The difference in oxygen saturation levels between the groups was about 3 percentage points instead of the 6 percentage points that had been planned. Therefore, this study actually compared saturation levels of about 89 to 97% with saturation levels of 91 to 97%; the results should be ascribed to these higher ranges. There is evidence that nurses tend to keep a baby's oxygen saturation level toward the higher end of the range,[7] which may account for the shift of both groups toward higher saturation levels than those targeted.

There was no significant difference between the oxygen-saturation groups in the primary outcome of severe retinopathy of prematurity or death before discharge. However, even with the relatively modest difference in oxygen saturation levels between the groups, the rate of severe retinopathy of prematurity was lower in the lower-oxygen-saturation group than in the higher-oxygen-saturation group (8.6% vs. 17.9%, $P<0.001$).

Moderate-to-severe bronchopulmonary dysplasia is defined as the need for supplemental oxygen in a very preterm infant at 36 weeks of postmenstrual age.[8] This trial also used a physiological definition of bronchopulmonary dysplasia, which calls for the F_IO_2 to be reduced at 36 weeks in order to determine whether supplemental oxygen is really required.[6] As in previous studies,[9] the rate of needed treatment with supplemental oxygen at 36 weeks among survivors was lower in the lower-oxygen-saturation group than in the higher-oxygen-saturation group ($P=0.002$). When the physiological definition of bronchopulmonary dysplasia was used, the rate of oxygen use at 36 weeks was not altered in the lower-oxygen-saturation group but it was reduced in the higher-oxygen-saturation group, with the result that the difference between the groups was no longer significant. The rate of the composite of death or bronchopulmonary dysplasia (according to either definition) by 36 weeks did not differ significantly between the groups.

There was weak evidence[10] of an increased rate of death before discharge in the lower-oxygen-saturation group ($P=0.04$). An association between lower oxygen-saturation targets and increased mortality has been reported previously in some[11] but not other[3,12] nonrandomized studies and was not observed in a previous randomized trial.[9] This is a most important outcome, but caution is warranted in interpreting this result. Additional research is needed to clarify this finding. There were no significant differences between the groups in short-term outcomes that have been associated with relative ischemia.

How do the results of this trial help neonatologists? They show that starting CPAP at birth in very preterm babies, even if it fails in some, has important benefits and no serious side effects. Predicting which babies will not have an adequate response to treatment with CPAP and should therefore receive early ventilation and surfactant should be a future goal. Targeting oxygen saturation levels is difficult, and a recommended oxygen saturation range that is effective yet safe remains elusive. A lower oxygen saturation level significantly reduces the incidence of severe retinopathy of prematurity but may increase the rate of death. Long-term follow-up is vital to determine whether either intervention was associated with neurodevelopmental problems.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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This article (10.1056/NEJMe1004342) was published on May 16, 2010, and updated on July 21, 2010, at NEJM.org.

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Hypoplastic Left Heart Syndrome

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Just 30 years ago, the newborn with hypoplastic left heart syndrome faced certain death. This congenital defect involves a rudimentary mitral valve and left ventricle, coupled with a hypoplastic aortic valve and ascending aorta.[1] Multistage surgical remediation of hypoplastic left heart syndrome, introduced in the 1980s, has led to survival rates that exceed 60%, and in this issue of the *Journal*, Ohye et al. report a further survival benefit with the use of a newly developed shunt.[2]

The fetus with hypoplastic left heart is able to survive until birth because of the unique fetal circulatory pattern. In the fetus with hypoplastic left heart syndrome, since fetal blood is oxygenated by the placenta, the right-heart and pulmonary circulation is usually sidetracked before birth, so the right heart may pinch hit for the left to serve the systemic circulation. Oxygenated blood entering the left atrium crosses the foramen ovale to the right heart and is pumped into the pulmonary artery. This blood then bypasses the defective ascending aorta and reaches the systemic circulation via a dilated ductus arteriosus (see Fig. 1 of the article by Ohye et al.[2]). Birth is a catastrophic event in hypoplastic left heart syndrome. Under normal circumstances, the foramen ovale and ductus close at birth to allow the newborn's blood to be oxygenated by means of the pulmonary circulation. In newborns with hypoplastic left heart syndrome, however, these changes effectively shut down the systemic circulation, causing right heart failure and death within a few days.

Hypoplastic left heart syndrome is a genetically heterogeneous disorder that affects 1 in 5000 live births.[3] About one third of cases occur in the context of a recognized genetic disorder such as Turner's syndrome (in which all or major parts of one sex chromosome are deleted) or Jacobsen's syndrome (in which the terminal part of 11q is deleted) or in the context of a monogenic disorder such as Noonan's or Holt–Oram's syndrome. Screening studies involving family members of nonsyndromic probands with hypoplastic left heart syndrome suggest that heritability is complex, encompassing various left ventricular outflow tract defects, and no single disease-causing gene or pathway has as yet been identified.[4]

In the early 1980s, Norwood and colleagues at the Children's Hospital of Philadelphia pioneered a three-stage surgical intervention for hypoplastic left heart syndrome.[5] Their goal was to establish a right-heart–based systemic circulation, using the Fontan procedure to create a separate pulmonary circulation, in which venous blood returns passively to the lungs. The first stage, known as the Norwood procedure, is the most difficult to perform and is associated with a high risk of death; it must be undertaken soon after birth to save the infant's life and prevent damage to the right heart and pulmonary vasculature. The procedure involves excising the atrial septum, so that oxygenated blood entering the left atrium crosses to the right heart; remodeling the ascending aorta, which is then patched into the proximal pulmonary artery, allowing the right ventricle to drive the systemic circulation; and establishing a separate conduit to deliver blood from the right ventricle to the pulmonary circulation.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 27, 2010 VOL. 362 NO. 21

Target Ranges of Oxygen Saturation in Extremely Preterm Infants

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network*

ABSTRACT

BACKGROUND

Previous studies have suggested that the incidence of retinopathy is lower in preterm infants with exposure to reduced levels of oxygenation than in those exposed to higher levels of oxygenation. However, it is unclear what range of oxygen saturation is appropriate to minimize retinopathy without increasing adverse outcomes.

METHODS

We performed a randomized trial with a 2-by-2 factorial design to compare target ranges of oxygen saturation of 85 to 89% or 91 to 95% among 1316 infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation. The primary outcome was a composite of severe retinopathy of prematurity (defined as the presence of threshold retinopathy, the need for surgical ophthalmologic intervention, or the use of bevacizumab), death before discharge from the hospital, or both. All infants were also randomly assigned to continuous positive airway pressure or intubation and surfactant.

RESULTS

The rates of severe retinopathy or death did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3% and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21). Death before discharge occurred more frequently in the lower-oxygen-saturation group (in 19.9% of infants vs. 16.2%; relative risk, 1.27; 95% CI, 1.01 to 1.60; P=0.04), whereas severe retinopathy among survivors occurred less often in this group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001). There were no significant differences in the rates of other adverse events.

CONCLUSIONS

A lower target range of oxygenation (85 to 89%), as compared with a higher range (91 to 95%), did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors. The increase in mortality is a major concern, since a lower target range of oxygen saturation is increasingly being advocated to prevent retinopathy of prematurity. (ClinicalTrials.gov number, NCT00233324.)

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This article (10.1056/NEJMoa0911781) was published on May 16, 2010, at NEJM.org.

N Engl J Med 2010;362:1959-69.

Retinopathy of prematurity is an important cause of blindness and other visual disabilities in preterm infants. The incidence of retinopathy of prematurity was increased with exposure to unrestricted oxygen supplementation in preterm infants in randomized, controlled trials performed in the 1950s.[1] In the 1960s, this increase resulted in the practice of restricting the fraction of inspired oxygen (FIO_2) to no more than 0.50, which was estimated to result in an excess of 16 deaths per case of blindness prevented.[2] More recent data suggest that levels of oxygen saturation previously thought to be at the upper end of the normal range may increase the risk of retinopathy of prematurity as compared with levels at the lower end of the normal range.[3-5] Oxygen toxicity may also increase the risk of death,[6,7] bronchopulmonary dysplasia,[8-10] periventricular leukomalacia,[11] cerebral palsy,[12] and other conditions. Although a multicenter observational study did not show a significant association between higher values for the partial pressure of arterial oxygen and retinopathy, a single-center cohort study involving transcutaneous oxygen monitoring provided support for an association between an increased risk of retinopathy[13] and exposure to arterial oxygen levels of 80 mm Hg or more.[14]

Pulse oximetry allows clinicians to continuously monitor levels of oxygen saturation and to target levels in a defined range. Associations between lower target levels of oxygen saturation and a lower incidence of retinopathy have been reported.[1-5] In a survey of 144 neonatal intensive care units (NICUs), the rate of retinal ablation surgery among very-low-birth-weight infants was increased among infants cared for in NICUs that used higher maximum target levels of oxygen saturation, as compared with infants in NICUs that used lower target levels. The rate of retinal ablation surgery was 3.3% in NICUs using target levels of 92% or higher and 1.4% in NICUs using target levels of less than 92%; the rate was 5.6% in NICUs using target levels of 98% or higher and 3.1% in NICUs using target levels of less than 98%.[3] In a retrospective study comparing outcomes at five NICUs, the incidence of severe retinopathy requiring ablation therapy was 27% in NICUs where the target saturation level was 88 to 98% and only 6% in NICUs where the target level was 70 to 90%.[3] Rates of death and cerebral palsy did not differ significantly among these NICUs. In three studies with a before-and-after design, the implementation of a policy of target levels of oxygen saturation of approximately 83 to 95% was associated with a substantial reduction in the incidence of retinopathy, as compared with the period before implementation of the policy; however, the actual levels of oxygen saturation achieved, mortality, and neurodevelopmental outcomes were not reported.[4,15,16] Although data from these studies suggest that maintenance of oxygenation at ranges lower than those previously used may decrease the incidence of retinopathy of prematurity, the safety of low target levels of oxygen saturation remains a concern.

We conducted the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a controlled, multicenter trial with a 2-by-2 factorial design, to compare two target levels of oxygen saturation and two ventilation approaches (continuous positive airway pressure [CPAP] initiated in the delivery room with a protocol-driven strategy of limited ventilation vs. intratracheal administration of surfactant with a protocol-driven strategy of conventional ventilation). The oxygen-saturation component of the trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation. The ventilation part of this factorial-design trial, which was used to control the ventilation approach and test other hypotheses, is reported elsewhere in this issue of the *Journal*.[17]

METHODS

STUDY DESIGN

The study was conducted as part of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The study was approved by the institutional review board at each participating site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Data collected at the study sites were transmitted to RTI International, which stored, managed, and analyzed the data for this

study. Written informed consent was obtained from the parent or guardian of each child before delivery.

PATIENTS

Infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation were eligible for enrollment at birth. Infants born in other hospitals and those known to have major congenital anomalies were excluded.

ENROLLMENT AND TREATMENT

Infants were enrolled from February 2005 through February 2009. Permuted-block randomization was used, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). Using sealed, opaque envelopes, we randomly assigned infants before birth to a target range of oxygen saturation of 85 to 89% (the lower-oxygen-saturation group) or 91 to 95% (the higher-oxygen-saturation group). Infants who were part of multiple births were randomly assigned to the same group.

Blinding was maintained with the use of electronically altered pulse oximeters (Masimo Radical Pulse Oximeter) that showed saturation levels of 88 to 92% for both targets of oxygen saturation, with a maximum variation of 3%. For example, a reading of 90% corresponded to actual levels of oxygen saturation of 87% in the group assigned to lower oxygen saturation (85 to 89%) and 93% in the group assigned to higher oxygen saturation (91 to 95%). A previous trial used a fixed 3% absolute oxygen-saturation variation throughout the entire range of saturation levels to keep caregivers unaware of study-group assignments and to separate levels of oxygen saturation in preterm infants,[18] but the algorithm used in the current trial differed, since the oxygen-saturation reading gradually changed and reverted to actual (nonskewed) values when it was less than 84% or higher than 96% in both treatment groups. Limits of 85% and 95% that would trigger an alarm in the delivery system were suggested, but they could be changed for individual patients.

Targeting of levels of oxygen saturation with altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the infant was breathing ambient air and did not require ventilator support or CPAP for more than 72 hours, whichever occurred first. Infants who were weaned to room air but who subsequently received oxygen supplementation before 36 weeks of postmenstrual age were placed back on the assigned study pulse oximeter. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age. Adjustments in supplemental oxygen to maintain the target level of oxygen saturation between 88 and 92% were performed by the clinical staff rather than the research staff.

Data on oxygen saturation were electronically sampled every 10 seconds and downloaded by the data center. Readings of levels of oxygen saturation that were pooled (i.e., not separated according to treatment group) were provided quarterly to each center for feedback on compliance. Actual data on oxygen saturation were not provided to the clinicians or researchers but are used exclusively in this article. For the ventilation part of this trial with a 2-by-2 factorial design, participants were randomly assigned to CPAP with a protocol-driven limited ventilation strategy or to prophylactic early administration of surfactant with a protocol-driven conventional ventilation strategy.[17]

ASSESSMENTS

Research nurses recorded all data using standardized definitions included in the trial's manual of operations. Data collection, excluding examinations to detect retinopathy of prematurity, was completed at discharge. All surviving infants were followed by ophthalmologists trained in the diagnosis of retinopathy of prematurity. Examinations began by 33 weeks of postmenstrual age and continued until the study outcome was reached or resolution occurred. Resolution was defined as fully vascularized retinas or immature vessels in zone 3 for two consecutive examinations in each eye. Threshold retinopathy of prematurity (called "new type 1 threshold" by the Early Treatment of Retinopathy Cooperative Group[19,20]) was diagnosed if any of the following findings were present: in zone 1, stage 3 retinopathy of prematurity, even without plus disease (i.e., two or more quadrants of dilated veins and tortuous arteries in the posterior pole), or plus disease with any stage of retinopathy of prematurity; in zone 2, plus disease with stage 2 retinopathy of prematurity or plus disease with stage 3 retinopathy of

prematurity. Surgical ophthalmologic intervention was recorded if any of the following occurred: laser therapy, cryotherapy, both laser therapy and cryotherapy, scleral buckling, or vitrectomy. The primary outcome was death before discharge or severe retinopathy as defined by threshold retinopathy, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy. The original study protocol specified a primary outcome of death before 36 weeks of postmenstrual age, but this was changed to death before discharge before any data analyses were performed. All other outcomes reported were prespecified, including assessment of the need for oxygen at 36 weeks of postmenstrual age[21] and safety outcomes.

STATISTICAL ANALYSIS

The analysis for the oxygen-saturation part of this factorial trial compared the percentage of infants in each treatment group in whom the primary outcome of severe retinopathy or death occurred. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. We performed a post hoc survival analysis with the use of a Cox proportional-hazards model to compare mortality in the two oxygen-saturation groups, assuming that there were no subsequent deaths among the infants who were discharged. In the analysis of all outcomes, the results were adjusted, as prespecified, for stratification according to study center and gestational age, as well as for familial clustering due to random assignment of infants who were part of multiple births to the same treatment group. To compare the actual oxygen-saturation values in the two treatment groups, the median value during oxygen supplementation was determined for each infant. Those values were plotted according to treatment group, and the medians of the resulting distributions were compared with the use of a rank-sum test.

An absolute between-group difference of 10 percentage points in the rate of the composite primary outcome was considered clinically important. The sample-size calculations were based on the rate of death or threshold retinopathy of 47% in the Neonatal Research Network for the year 2000. We increased the sample size by a factor of 1.12 to allow for infants who were part of multiple births to be randomly assigned to the same treatment (since this introduced a clustering effect into the design), and we increased the sample size by an additional 17% to adjust for attrition after hospital discharge. We increased the sample size further to minimize type I error with the use of a conservative 2% level of significance. The result was a target sample of 1310 infants. The study was not powered to detect an interaction effect between the two factorial parts of the study.

Figure 1 (facing page). Screening, Randomization, and Primary Outcome.

The numbers shown exclude infants of women who were screened during pregnancy but whose babies were not subsequently born at a study center between 24 weeks 0 days and 27 weeks 6 days of gestation. The outcome of severe retinopathy of prematurity (ROP) could not be determined in some infants because of loss to follow-up. CPAP denotes continuous positive airway pressure.

Analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. All analyses were conducted at the data center. Two-sided P values of less than 0.05 were considered to indicate statistical significance. Analyses of secondary outcomes did not include adjustment for multiple comparisons; however, for the 46 planned analyses of secondary outcomes according to treatment group, we would expect no more than three tests to have P values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for predefined outcomes. Although these tests were not adjusted for multiple comparisons, we would expect no more than two tests per stratum to have P values of less than 0.05 on the basis of chance alone.

An independent data and safety monitoring committee appointed by the director of the National Institute of Child Health and Human Development reviewed the primary outcomes, adverse events, and other interim results at approximately 25%, 50%, and 75% of planned enrollment. In addition, the data and safety monitoring committee, at the request of the investigators, evaluated the data on oxygen saturation to evaluate compliance with the protocol. The Lan–DeMets spend-

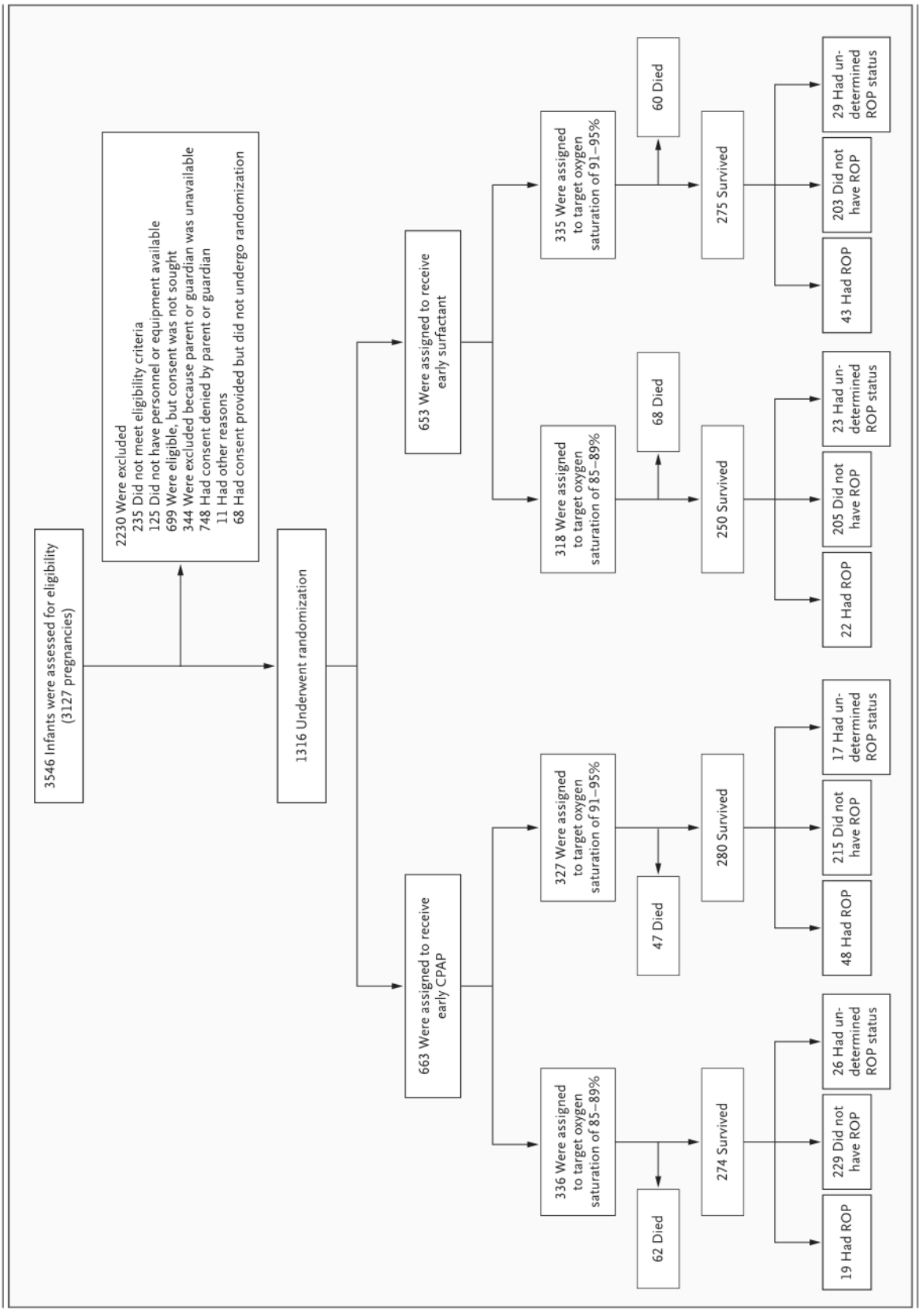

Table 1. **Baseline Characteristics of the Patients.**

Characteristic	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)
Birth weight — g	836±193	825±193
Gestational age — wk	26±1	26±1
Male sex — no./total no. (%)	341/654 (52.1)	371/662 (56.0)
Race or ethnic group — no./total no. (%)†		
Non-Hispanic white	242/654 (37.0)	279/662 (42.1)
Non-Hispanic black	257/654 (39.3)	232/662 (35.0)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other or unknown	23/654 (3.5)	24/662 (3.6)
Maternal use of antenatal corticosteroids — no./total no. (%)		
Any	633/654 (96.8)	632/661 (95.6)
Full course	477/651 (73.3)	462/658 (70.2)
Apgar score <3 at 5 min — no./total no. (%)	34/654 (5.2)	24/662 (3.6)
Surfactant treatment — no./total no. (%)	531/653 (81.3)	558/660 (84.5)
Multiple birth — no./total no. (%)	161/654 (24.6)	176/662 (26.6)

* Plus–minus values are means ±SD. P>0.05 for all comparisons.
† Race or ethnic group was reported by the mother or guardian of each child.

ing functions with Pocock and O'Brien–Fleming boundaries were used to develop stopping rules for interim safety and efficacy monitoring, respectively. In the final analysis, the nominal level of significance was 0.05. The monitored safety outcomes included death, pneumothorax, intraventricular hemorrhage, and a combination of any of these events.

RESULTS

CHARACTERISTICS OF THE STUDY SAMPLE

We enrolled 1316 infants in the study (Fig. 1). When 247 infants had been enrolled, enrollment was temporarily suspended on the basis of the recommendation of the data and safety monitoring committee and the decision of the director of the National Institute of Child Health and Human Development because of concern that readings of levels of oxygen saturation often exceeded the target levels. Separation of the oximetry data according to whether patients were breathing ambient air or receiving oxygen supplementation addressed this concern, because infants who did not require supplemental oxygen accounted for a large proportion of the high saturation levels. Resumption of enrollment was approved. The baseline characteristics of the two treatment groups were similar (Table 1).

PRIMARY OUTCOME

The rate of the composite primary outcome, severe retinopathy or death before discharge, did not differ significantly between the lower-oxygen-saturation group and the higher-oxygen-saturation group (28.3 and 32.1%, respectively; relative risk with lower oxygen saturation, 0.90; 95% confidence interval [CI], 0.76 to 1.06; P=0.21) (Table 2). Although the trial was not powered to detect an interaction between the level of oxygen saturation and the ventilation intervention, we prospectively planned to evaluate this interaction, and no significant interaction was found (P=0.57). Death before discharge occurred in 130 of 654 infants in the lower-oxygen-saturation group (19.9%) as compared with 107 of 662 infants in the higher-oxygen-saturation group (16.2%) (relative risk with lower oxygen saturation, 1.27; 95% CI, 1.01 to 1.60; P=0.04; number needed to harm, 27). The distribution of the major causes of death did not differ significantly between the two groups (see Table 1 in the Supplementary Appendix, available with the

Table 2. **Major Outcomes.***

Outcome	Lower Oxygen Saturation (N=654)	Higher Oxygen Saturation (N=662)	Adjusted Relative Risk (95% CI)
	no./total no. (%)		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76–1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37–0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01–1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99–1.63)
BPD, defined by use of supplemental oxygen, at 36 wk	203/540 (37.6)	265/568 (46.7)	0.82 (0.72–0.93)
BPD, defined by use of supplemental oxygen, or death by 36 wk	317/654 (48.5)	359/662 (54.2)	0.91 (0.83–1.01)
BPD, physiological definition, at 36 wk†	205/540 (38.0)	237/568 (41.7)	0.92 (0.81–1.05)
BPD, physiological definition, or death by 36 wk†	319/654 (48.8)	331/662 (50.0)	0.99 (0.90–1.10)
Intraventricular hemorrhage, grade 3 or 4‡	83/630 (13.2)	81/640 (12.7)	1.06 (0.80–1.40)
Intraventricular hemorrhage, grade 3 or 4, or death‡	179/653 (27.4)	156/661 (23.6)	1.18 (0.99–1.42)
Periventricular leukomalacia	24/631 (3.8)	30/641 (4.7)	0.83 (0.49–1.42)
Periventricular leukomalacia or death	149/654 (22.8)	132/662 (19.9)	1.18 (0.96–1.45)
Necrotizing enterocolitis, stage ≥2§	76/641 (11.9)	70/649 (10.8)	1.11 (0.82–1.51)
Necrotizing enterocolitis, stage ≥2, or death§	176/654 (26.9)	155/662 (23.4)	1.18 (0.98–1.43)
Pneumothorax	47/654 (7.2)	43/662 (6.5)	1.12 (0.74–1.68)
Postnatal corticosteroids for BPD	61/636 (9.6)	69/644 (10.7)	0.91 (0.67–1.24)
Death			
By 7 days	41/654 (6.3)	38/662 (5.7)	1.11 (0.72–1.72)
By 14 days	64/654 (9.8)	56/662 (8.5)	1.20 (0.84–1.70)
Late-onset sepsis	228/624 (36.5)	226/634 (35.6)	1.03 (0.89–1.18)
Late-onset sepsis or death	300/654 (45.9)	291/662 (44.0)	1.05 (0.94–1.18)
Patent ductus arteriosus	307/641 (47.9)	324/648 (50.0)	0.96 (0.86–1.07)
Treatment for patent ductus arteriosus			
Medical	219/634 (34.5)	233/645 (36.1)	0.95 (0.82–1.09)
Surgical	73/641 (11.4)	68/648 (10.5)	1.09 (0.80–1.48)
Any air leaks in first 14 days	51/654 (7.8)	42/662 (6.3)	1.23 (0.83–1.83)

* Values were adjusted for stratification factors (study center and gestational-age group) as well as for familial clustering. BPD denotes bronchopulmonary dysplasia.
† The physiological definition of BPD includes, as a criterion, the receipt of more than 30% oxygen or the need for positive pressure support at 36 weeks or, in the case of infants requiring less than 30% oxygen, the need for any oxygen at 36 weeks after an attempt at oxygen withdrawal.
‡ There are four grades of intraventricular hemorrhage; higher grades indicate more severe bleeding.
§ There are three stages of necrotizing enterocolitis; higher stages indicate more severe necrotizing enterocolitis.

full text of this article at NEJM.org). Similar results were observed for both gestational-age strata. Survival analysis with the use of the unadjusted Kaplan–Meier method (Fig. 2) and a Cox proportional-hazards model produced similar results (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07). The rate of severe retinopathy among survivors who were discharged or transferred to another facility or who reached the age of 1 year was lower in the lower-oxygen-saturation group (8.6% vs. 17.9%; relative risk, 0.52; 95% CI, 0.37 to 0.73; P<0.001; number needed to treat, 11). Although

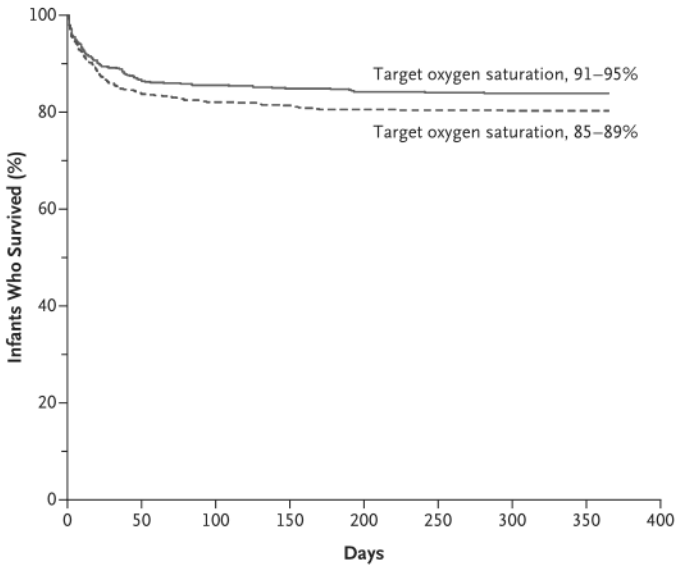

Figure 2. Kaplan–Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life.

Cox proportional-hazards analysis indicated that there was an increased hazard of death in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (hazard ratio, 1.28; 95% CI, 0.98 to 1.68; P=0.07). The analysis assumed that infants who were discharged or transferred from the hospital survived to 1 year of age.

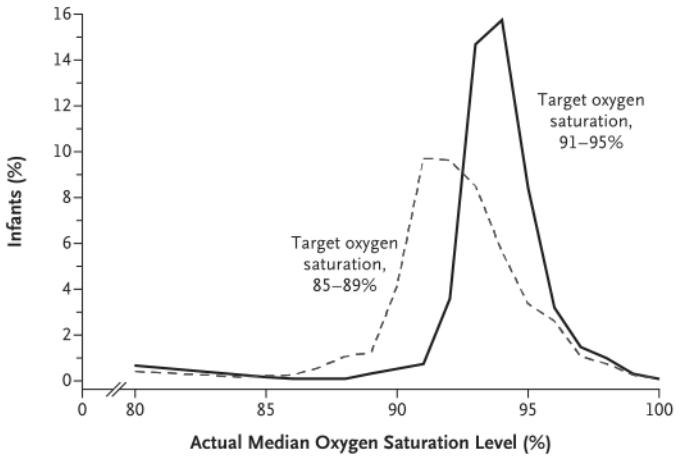

Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups.

The medians of the distributions were significantly different on the basis of a rank-sum test (P<0.001). The 80% level of oxygen saturation shown includes all values at or below 80%.

use of bevacizumab was among the criteria for this outcome, only three infants received bevacizumab, and these infants also had threshold retinopathy or surgical intervention for retinopathy. Three ophthalmologists adjudicated results for the patients who did not meet the criteria for retinopathy, and the results were materially unchanged (Table 2 in the Supplementary Appendix).

SECONDARY OUTCOMES

The rate of oxygen use at 36 weeks was reduced in the lower-oxygen-saturation group as compared with the higher-oxygen-saturation group (P=0.002), but the rates of bronchopulmonary dysplasia among survivors, as determined by the physiological test of oxygen saturation at 36 weeks, and the composite outcome of bronchopulmonary dysplasia or death by 36 weeks did not differ significantly between the treatment groups. Other prespecified major outcomes also did not differ significantly between the two groups (Table 2).

The median level of oxygen saturation in infants who were receiving oxygen supplementation in the two treatment groups differed substantially but, as expected, there was considerable overlap (Fig. 3). The actual median levels of oxygen saturation were slightly higher than targeted levels in both treatment groups. The duration of oxygen supplementation was shorter in the lower-oxygen-saturation group, but the duration of mechanical ventilation, CPAP, and nasal synchronized intermittent mandatory ventilation did not differ significantly (Table 3 in the Supplementary Appendix). Other measures of resource use also did not differ significantly between the two groups.

DISCUSSION

In this multicenter, randomized trial, we found no significant difference in the primary outcome — severe retinopathy or death — between infants randomly assigned to a lower target range of oxygen saturation (85 to 89%) and those assigned to a higher target range (91 to 95%). Assessment of the individual components of the primary outcome showed that the lower target range of oxygen saturation increased the risk of in-hospital death, whereas it reduced the risk of severe retinopathy among survivors. These results were observed even though there was substantial overlap of actual levels of oxygen saturation between the two treatment groups. Previous trials of targeting of levels of oxygen saturation have shown similar difficulties in maintaining levels of oxygen saturation within a narrow target range.[18,22] Longer follow-up will be required to determine

the effects of lower target ranges of oxygen saturation on functional visual and neurodevelopmental outcomes.

Despite the increase in mortality when restrictive oxygen supplementation was used in the 1950s and 1960s and the limited data from observational studies,[3-5,15,16] it is becoming common practice to use lower target ranges of oxygen saturation with the goal of reducing the risk of retinopathy of prematurity.[23] The results of this large randomized trial to test the effect of lower versus higher target ranges of oxygen saturation, in conjunction with the results of previous studies, add to the concern that oxygen restriction may increase the rate of death among preterm infants. The combined risk difference observed in the trials from the 1950s was an absolute increase in in-hospital mortality of 4.9 percentage points in the oxygen-restricted group,[1] which is close to the absolute increase of 3.7 percentage points in the rate of death before discharge in the lower-oxygen-saturation group that was observed in the current trial.

Randomized trials of oxygen restriction in preterm infants at least 2 weeks after birth[18] or after moderately severe retinopathy developed[22] did not show an increased risk of death or a significantly reduced risk of retinopathy in the lower-oxygen-saturation groups. However, the lower target ranges of oxygen saturation in these trials — 91 to 94% in one trial and 89 to 94% in the other — were closer to the target range in our higher-oxygen-saturation group. The increase in mortality in our trial may be related to the lower target ranges of levels of oxygen saturation, the use of oxygen restriction started soon after birth, or both. A meta-analysis of early restriction of oxygen supplementation based on trials from the 1950s to the 1970s showed a reduction in severe retinopathy (relative risk, 0.19; 95% CI, 0.07 to 0.50) with a nonsignificant trend toward increased mortality.[24] These trials were performed by limiting the FIO_2 concentration usually to less than 0.50, at a time before the continuous monitoring of arterial oxygen saturation was possible. To our knowledge, no other randomized, controlled trials of different target ranges of oxygen saturation in supplementation initiated soon after birth have been performed since the availability of continuous transcutaneous monitoring of oxygen saturation. Like the meta-analysis[24] and most nonrandomized studies,[3-5,15,16] our trial confirmed that lower target ranges of oxygenation result in a large reduction in the incidence of severe retinopathy among survivors. However, our data suggest that there is one additional death for approximately every two cases of severe retinopathy that are prevented. Several ongoing trials across the world address the same intervention tested in the current trial.[25]

In summary, a target range of oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, did not affect the combined outcome of severe retinopathy or death, but it increased mortality while substantially decreasing severe retinopathy among survivors. At the present time, caution should be exercised regarding a strategy of targeting levels of oxygen saturation in the low range for preterm infants, since it may lead to increased mortality.

Supported by grants (U10 HD21364, U10 HD21373, U10 HD21385, U10 HD21397, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27880, U10 HD27871, U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40461, U10 HD40492, U10 HD40498, U10 HD40521, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD53119, and U10 HD53124) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, cofunding from the National Heart, Lung, and Blood Institute, and grants (M01 RR30, M01 RR32, M01 RR39, M01 RR44, M01 RR54, M01 RR59, M01 RR64, M01 RR70, M01 RR80, MO1 RR125, M01 RR633, M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 RR25008, UL1 RR24139, UL1 RR24979, and UL1 RR25744) from the National Institutes of Health.

Dr. Van Meurs reports receiving reimbursement for travel expenses from Ikaria Holdings. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank our medical and nursing colleagues and the infants and their parents who agreed to take part in this study.

APPENDIX

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From:	Devaney, Stephanie (NIH/OD) [E]
To:	Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]
Subject:	FW: SUPPORT study issue still unresolved
Date:	Thursday, April 25, 2013 11:08:29 AM

From: Abel, Kathy (NIH/OD) [E]
Sent: Thursday, April 25, 2013 11:08 AM
To: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: SUPPORT study issue still unresolved

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, April 25, 2013 10:26 AM
To: Hudson, Kathy (NIH/OD) [E]
Subject: Fwd: SUPPORT study issue still unresolved

Spoke with Bill, he's on it. (b)(5)

(b)(5)

Sent from my iPhone

Begin forwarded message:

From: "Corr, Bill (HHS/IOS)" <Bill.Corr@hhs.gov>
Date: April 25, 2013 7:51:10 AM EDT
To: "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>
Subject: RE: SUPPORT study issue still unresolved

Francis,
Heading to SCIF, will try to reach you before 8:30am.

From: Collins, Francis (NIH/OD) [E] [mailto:collinsf@od.nih.gov]
Sent: Wednesday, April 24, 2013 9:54 PM
To: Corr, Bill (HHS/IOS)
Subject: SUPPORT study issue still unresolved
Importance: High

Hi Bill,

(b)(5)

(b)(5)

Do you have a few minutes early tomorrow to discuss this? I could call anytime before 8:30 AM.

Thanks, and sorry to trouble you,

Francis

From:	Hudson, Kathy (NIH/OD) [E]
To:	Lewis, Caya (HHS/IOS); Palm, Andrea (HHS/IOS)
Cc:	Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Devaney, Stephanie (NIH/OD) [E]; McGarey, Barbara (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Burklow, John (NIH/OD) [E]; White, Pat (NIH/OD) [E]; Howard, Sally (HHS/IOS); Collins, Francis (NIH/OD) [E]; Horowitz, David (HHS/OGC)
Subject:	NIH two pager SUPPORT 042413 11PM
Date:	Wednesday, April 24, 2013 11:40:45 PM
Attachments:	NIH two pager SUPPORT 042413 11PM.docx

Caya,

You asked for a two pager on the support study by 1 pm tomorrow. Please accept our slightly longer (3.15 pages) that has not undergone extensive review here but please know that the nih team is all standing firmly together about our views on this. (b)(5)

(b)(5)

kathy

NIH's Concerns About the OHRP Complaint Against the SUPPORT Study
April 24, 2013

(b)(5)

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

(b)(5)

NIH's Concerns about OHRP's Complaint

(b)(5)

Withheld pursuant to exemption

(b)(5)

of the Freedom of Information and Privacy Act

From:	Hudson, Kathy (NIH/OD) [E]
To:	Devaney, Stephanie (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject:	Fwd: SUPPORT study issue still unresolved
Date:	Wednesday, April 24, 2013 10:18:03 PM
Attachments:	NEJM 4-17-13 Editorial.doc ATT00001.htm

FYI and not to distribute.

Kathy Hudson, Ph.D.
Deputy Director for Science, Outreach, and Policy
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301 496 1455
kathy.hudson@nih.gov

Begin forwarded message:

From: "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>
Date: April 24, 2013, 9:53:48 PM EDT
To: "Corr, Bill (HHS/IOS)" <Bill.Corr@hhs.gov>
Subject: SUPPORT study issue still unresolved

Hi Bill,

(b)(5)

Do you have a few minutes early tomorrow to discuss this? I could call anytime before 8:30 AM.

Thanks, and sorry to trouble you,

Francis

NEW ENGLAND JOURNAL OF MEDICINE

EDITORIAL

Informed Consent and SUPPORT

Jeffrey M. Drazen, M.D., Caren G. Solomon, M.D., M.P.H., and Michael F. Greene, M.D.

April 17, 2013DOI: 10.1056/NEJMe1304996

In the summer of 1963, the nation watched in sadness as Patrick Bouvier Kennedy, the youngest child of President John F. Kennedy and First Lady Jacqueline Bouvier Kennedy, was born prematurely and then died of lung disease 2 days later at Children's Hospital in Boston. Even now, it is common knowledge that children born prematurely are at high risk for death.

So it is easy to imagine the stress when, in 2005, your new baby decides to come into the world after only 6 months of gestation, long before your pregnancy has reached term. You know that extremely premature babies like yours may not survive, but you are reassured that you are giving birth at an academic medical center with a sophisticated nursery for premature newborns and with physicians who have extensive experience with very preterm infants. Decades of study and refining practice have resulted in major improvements in the care of premature infants; now most babies weighing a kilogram or more, and many weighing less than this, survive. This progress has come through careful research in multiple aspects of neonatal care, but many questions remain regarding practice that will maximize survival and minimize the long-term sequelae resulting from surviving severe prematurity. Without research studies your neonatologist would simply be guessing about what is best rather than knowing what is best for your child.

The physicians in the nursery ask you to allow your very premature baby to participate in a research study, called the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), part of which is focused on the amount of supplemental oxygen they will give to your baby. They orally explain the study to you and ask you to sign an informed-consent document; it is six pages of single-spaced typescript.

Premature babies often require supplemental oxygen; what was not known in 2005 was exactly how much oxygen to give. The doctors knew that maintaining very high oxygen levels in the blood might cause retinopathy of prematurity (ROP), or abnormal growth of blood vessels in the eyes, which can damage the retinas and impair vision. The informed-consent form notes the higher risk of ROP that is associated with prolonged exposure to supplemental oxygen but states that “the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known” and also notes that “the use of lower saturation ranges may result in a lower incidence of severe ROP.” Clinical practice at the time (and that recommended in the 2002 and 2007 guidelines of the American Academy of Pediatrics,[1,2] on whose guidelines committee one of us served) was to target values for the partial pressure of arterial oxygen anywhere between 50 and 80 mm Hg, consistent with oxygen saturations measured by pulse oximetry between 85% and 95%. Among the clinical

questions addressed by SUPPORT was whether targeting the upper or lower end of this range might result in better outcomes for very preterm infants.

The study was conceived in 2003, initiated in 2005, and completed in 2009. Trials addressing the same clinical question were initiated in 2006 in the United Kingdom, Australia, and New Zealand (Benefits of Oxygen Saturation Targeting [BOOST II]), indicating the importance of the question.[3] For a baby not enrolled in any of these trials, the specific range of oxygen saturation targeted within these broader guidelines was left to the discretion of the child's physician, who lacked data to guide decision making.

The consent document for SUPPORT that you have been handed spells this out clearly and succinctly: “The babies in the lower range group will have a target saturation of 85–89%, while the babies in the higher range group will have a target saturation of 91–95%. All of these saturations are considered normal ranges for premature infants.” You sign the form, and your child enters the study. The same process was also taking place with parents of newborn extremely premature infants at multiple centers across the country.

After 5 years and more than 1300 babies studied, the data from SUPPORT are published in 2010 in the *Journal*.[4] The data show that, even within the recommended oxygen saturation range, babies with a higher oxygen saturation target had a higher risk of ROP, and those with a lower saturation target had a higher risk of death. With this new information, the investigators in the BOOST II trials in the United Kingdom and Australia review their preliminary data and discover that lower oxygen saturations in their trials are also associated with a higher rate of death.[3] These findings changed medical practice at many centers.

There was no way for you as a parent of a child in SUPPORT to know what the answer would be before your child participated. The study made clear that higher oxygen saturations within the then-recommended range increased the risk of retinopathy but decreased the risk of death. This is how new medical knowledge is gained. The story should have ended there, but it didn't.

In 2011, the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services began an investigation into the informed-consent process used when newborns were enrolled in SUPPORT. Their investigation concluded with a 13-page letter of determination sent to the SUPPORT lead center on March 7, 2013 (provided with a sample informed-consent form in the Supplementary Appendix, available with the full text of this article at NEJM.org). The OHRP reached the following conclusion: “It was alleged, and we determine, that the IRB [institutional review board] approved informed consent documents for this study failed to include or adequately address the following basic element required by HHS [Health and Human Services] regulations at 45 CFR 46.116(a): Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts.”

This response is disappointing, because it does not take into account either the extent of clinical equipoise at the time the study was initiated and conducted or that the consent form, when viewed in its entirety, addressed

the prevalent knowledge fairly and reasonably. At the time, as explained in the principal investigator's response to the allegations and in a related letter to the editor in the *Journal*[5] there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent from parents of participating infants. Through hindsight (and essentially faulting investigators for not informing parents up front of a risk later uncovered by the trial itself), the OHRP investigation has had the effect of damaging the reputation of the investigators and, even worse, casting a pall over the conduct of clinical research to answer important questions in daily practice.

Clinical research is crucial if we are to advance medical science. Clinical investigators acted in good faith to design a trial to address an important question. An informed-consent document was drafted and approved by institutional review boards of participating centers before the work was begun. The OHRP has a duty to investigate questions of research impropriety, but we strongly disagree with their determination of inadequate informed consent in this case.

The results of SUPPORT have been critical in informing treatment decisions for extremely preterm infants. When babies like Patrick Bouvier Kennedy are born today, their chances of survival to adulthood are greatly improved, thanks to research made possible by thousands of parents and their children. We are dismayed by the response of the OHRP and consider the SUPPORT trial a model of how to make medical progress.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article was published on April 17, 2013, at NEJM.org.

Source Information

From the Massachusetts General Hospital, Boston (M.F.G.).

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]; Rowe, Mona (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Guttmacher, Alan (NIH/NICHD) [E]
Subject: RE: NIH memo on SUPPORT study
Date: Wednesday, April 24, 2013 5:47:36 PM
Attachments: Final Support Internal.docx

This is a document that we had previously worked on at NICHD– the issues at hand is that the AAP Guidelines for Perinatal Care were to target sats 85-95%. Thus, since a clinical guideline, there was not evidence at either end that mortality was at issue.

Let me know if you need more documentation.

Thanks for your help
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 5:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: RE: NIH memo on SUPPORT study

We don't really have a template and not enough time to develop one so send whatever you have rose and amy and I will work to get something ready to send downtown

---

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, April 24, 2013 5:36 PM
To: Hudson, Kathy (NIH/OD) [E]; Patterson, Amy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: Re: NIH memo on SUPPORT study

Amy-
Do you have a template?
Thanks
Rose
Rosemary D. Higgins

Program Scientist for the NICHD Neonatal Research Network

From: Hudson, Kathy (NIH/OD) [E]
Sent: Wednesday, April 24, 2013 05:34 PM
To: Patterson, Amy (NIH/OD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: FW: NIH memo on SUPPORT study

That one pager can now be 2 but can I get a draft tonight???

From: Lewis, Caya (HHS/IOS)
Sent: Wednesday, April 24, 2013 5:32 PM
To: Hudson, Kathy (NIH/OD) [E]
Cc: Devaney, Stephanie (NIH/OD) [E]
Subject: NIH memo on SUPPORT study
Importance: High

Kathy,

Thanks for your time earlier today on this.

(b)(5)

Thanks,

Caya

Caya B. Lewis, MPH
Counselor for Science & Public Health
Office of the Secretary, DHHS

What is the SUPPORT Study?

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) study was a large clinical trial that sought to determine how best to deliver oxygen to very small preterm infants and determine the ideal oxygen saturation targets for these very fragile newborns. The study compared the traditional means of providing oxygen, ventilator therapy with surfactant, to continuous positive airway pressure (CPAP), in which air is blown through a preterm infant's nostrils to gently inflate the lungs. When the study began, the standard treatment was to maintain oxygen levels in the range of 85 to 95 percent. The researchers sought to identify within this standard range the percentage of oxygen saturation that would minimize the risk of retinopathy of prematurity. Previous studies had shown that prolonged exposure to high levels of oxygen could increase the risk of retinopathy of prematurity, a complication of oxygen therapy that affects the retina and can sometimes result in vision loss. The study was divided into two arms, each of which proceeded at the same time, in the same group of infants. In the first arm, each infant had a 50 percent chance of receiving higher oxygen target saturation levels, and a 50 percent chance of receiving lower levels. In the second arm, each infant had a 50 percent chance of receiving oxygen by CPAP and a 50 percent chance of being assigned to the ventilator group.

What did the SUPPORT Study find?

The researchers found that the higher range increased the chances of survival but also increased the chances for ROP. This unexpected but critical finding informed clinical practice. The researchers also concluded that CPAP therapy was as effective as ventilator therapy, and resulted in fewer complications.

How did mortality rates from the study compare to those of infants not in the study?

Infants in the study had a lower mortality rate than those not enrolled. Even after adjusting for characteristics of the non-enrolled infants, such as poorer health, infants in the study were still at no greater risk of death and other conditions associated with extreme prematurity.

Percent Mortality:	
Higher saturation group	16.2 percent
Lower saturation group	19.9 percent
Infants treated outside of study	23.1 percent
Non-enrolled/Eligible patients	24.1 percent

Had the researchers anticipated a lower survival rate for the infants in the lower oxygen range?

No. The finding of a lower survival rate for those at the lower range was not anticipated or expected. At the time of the study, clinical practice for providing oxygen to very preterm babies varied widely. A target range of 85-95 percent was generally standard clinical practice and in 2007 was recommended by the American Academy of Pediatrics. In fact, at the time, emerging research showed that providing oxygen at the lower end of the acceptable range reduced the

risk of retinopathy without increasing the risk of death and neurodevelopmental impairment. As a result, physicians were starting to use the lower oxygen range to treat very preterm babies.

Has the Office for Human Research Protections (OHRP) criticized the design or rationale for the study?

It is critical to note that the treatments or the rationale of the study has never been in question by the Office for Human Research Protections.

What had OHRP objected to?

The OHRP cited the study for not including language, specifically in the risk/benefit section of the consent form, about research conducted in the 1950s suggesting the risk of death was higher with oxygen restriction.

Why had the researchers not included this language?

The older ROP studies were conducted before the widespread use of ventilators, pulse oximetry, and other sophisticated oxygen monitoring and measurement devices. The risk/benefit description under the oxygen saturation section of the consent form included language that reflected the available information/knowledge/data the oxygen administered at the lower saturation range reduced the risk of retinopathy. Since the current research had not shown a higher risk of death and neurodevelopmental impairment at any of these saturation levels (85-95%), the study authors did not list death and neurodevelopmental impairment as potential risks.

Were parents adequately informed of the study risks?

In addition to the consent form, representatives of the study explained the purpose of the research and its potential risks and benefits to parents and responded to their questions and concerns.

Has the OHRP expressed any additional concerns with the study?

In an interview with the New York Times (but not in the original letter to the Principal Investigator's institution, the University of Alabama), the Director of OHRP, Jerry Menikoff said: "Based on their very hypothesis, they were thinking that there might well be a difference…Being in the higher end [of the oxygen saturation range] should have put you at greater risk of developing eye disease." The parents were informed in the consent form that their children would be assigned at random to the higher or lower range. They were also told that they believed children at the lower range would be less likely to develop ROP. However, it was not explicitly stated that children at the higher range might be more likely to develop ROP.

In addition to the consent form, were there any other safeguards to ensure that the infants would receive the optimal care?

Attending physicians were allowed to override the settings if they thought their patients were in danger, and provide either more or less oxygen if they thought that following either course was in their patients' best interest. In addition, attending physicians and parents were free to ask that their children be withdrawn from the study at any time.

What is the purpose of the Neonatal Research Network (NRN)?

The NRN, which is currently composed of 18 medical research institutions, was established in 1986 to conduct clinical trials and observational studies in neonatal medicine to help reduce infant morbidity and mortality, and promote healthy outcomes.

Consistent with this mission, between 2000 and 2009, deaths of preterm infants declined 5.5%, from 109.75 per 1,000 live births to 103.48. Death rates for "early" preterm infants, those born before 32 weeks, declined 4.9% from 180.95 to 172.15 per 1,000 live births. In addition, NRN findings have helped to change clinical practice and improve outcomes for premature infants, such as:

- ✓ Identifying a safe way to protect newborns whose brains were getting insufficient oxygen
- ✓ Showing that providing additional Vitamin A to infants under 1,000 grams significantly reduced their risk of death or getting chronic lung disease
- ✓ Showing that giving intravenous immune globulin to reduce hospital-acquired infections in very low birthweight infants, actually increased rates of an often fatal intestinal condition in newborns
- ✓ Showing that giving additional glutamine, an amino acid, to extremely low birthweight infants did not reduce their risk of death or sepsis

Carr, Sarah (NIH/OD) [E]

From: Carr, Sarah (NIH/OD) [E]
Sent: Saturday, April 13, 2013 6:57 PM
To: Borror, Kristina C (HHS/OASH)
Subject: RE: UAB's response

Thanks, Kristina, and also for taking time to confer with us yesterday.

From: Borror, Kristina C (HHS/OASH)
Sent: Friday, April 12, 2013 4:17 PM
To: Patterson, Amy (NIH/OD) [E]; Carr, Sarah (NIH/OD) [E]; Stagnitto, Maria (NIH/OD) [E]; Hardy, Ann (NIH/OD) [E]; Gordon, Valery (NIH/OD) [E]
Cc: Menikoff, Jerry (HHS/OASH)
Subject: UAB's response

UAB's response is attached.

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Office of the Vice President for Research and Economic Development

March 22, 2013

Lisa R. Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight
Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

RE: Research Project entitled "The Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
Principal Investigator: Dr. Waldemar Carlo
HHS Protocol Number: 2U10HD034216

Dear Ms. Buchanan:

This letter is in response to your correspondence dated February 8, 2013 (and subsequent revision dated March 7, 2013) regarding the project referenced above. I am in receipt of a letter from the investigators of the NICHD Neonatal Research Network and authors of the SUPPORT Study Group. Allow me to provide an excerpt from that correspondence:

> The investigators of the NICHD Neonatal Research Network and authors of the SUPPORT Study Group would like to first thank OHRP for presenting its concerns clearly and giving us an opportunity to share our thinking about these issues. The Neonatal Research Network investigators are committed to the highest standards of ethical conduct in our human subjects' research, especially where vulnerable participants are concerned. Please ... let us know if we can discuss any of the issues by conference call at your convenience. We welcome the opportunity to engage in a constructive dialogue with OHRP to ensure that if there are opportunities to improve our research practices, we will identify them and incorporate them into our program going forward.

OHRP's letter requested that UAB "provide a plan that the IRB will use to ensure that approved informed consent documents include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a)". The following actions have already been implemented:

- The Office of the Institutional Review Board (OIRB) has revised the sample consent form (see Appendix I) provided to investigators. Information has been added to the Risks and Discomforts section to instruct investigators to include the specific risks of all arms even if those procedures fall within the parameters of standard of care.

- Checklists used by OIRB staff members to ensure both regulatory and institutional requirements are met prior to the IRB approval of a study have been refined to ensure inclusion of all of the basic elements of

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consent as required by HHS regulations at 45 CFR 46.116(a). The New Protocol Checklist is attached as Appendix II.

- OIRB staff members who coordinate the reviews of research protocols have been reminded that the risks of all study arms must be described in the consent document, even when those arms fall within the parameters of standard of care.

We believe the steps described above will ensure that approved informed consent documents will include and adequately address the basic elements of consent as required by HHS regulations at 45 CFR 46.116(a). The UAB OIRB continually seeks ways to improve its already strong program of human research protection and is appreciative of OHRP's recommendations and guidance.

Please do not hesitate to contact me if OHRP has questions or suggestions in this regard.

Sincerely,

Richard B. Marchase, Ph.D.
Vice President for Research and Economic Development

cc: Ferdinand Urthaler, MD, Chair, UAB IRBs
Jonathan Miller, Director, UAB Office of the IRB

Appendix I – UAB IRB Sample Informed Consent Document

Sample Consent Form

It is impossible to address all scenarios for the many types of research protocols conducted by UAB researchers. This sample is designed to assist you in the preparation of consent forms. It is intended to show language preferred by the UAB IRB to address the essential elements of informed consent. In many cases, the sample language will need to be modified, deleted, or expanded for the particular study.

Shaded paragraphs like this one are Instructions for you, the writer. Do not include them in the consent form you submit. If the instructions indicate that specific language applies to your protocol, the specific language will be shown below the instructions outside of the shaded paragraph.

Use this sample consent form as a guide for obtaining consent and/or assent from participants 14 years of age and older.

Formatting Instructions

- Use a 12 pt font for the consent form.
- Write the consent form in the 2nd person (i.e., you) and keep the pronoun usage consistent throughout.
- Use *Page X of Y* numbering on each page.
- Leave an area approximately 1 inch by 2 inches on the bottom of the first page for the IRB approval stamp.

Use understandable, non-technical language at an 8th-grade or lower reading level.

- Readability statistics can be displayed in Microsoft Word. Search Microsoft Office Help for "readability statistics" for further instructions.

DELETE THIS FIRST PAGE OF INFORMATION
IF YOU ARE USING THIS DOCUMENT
TO CREATE YOUR CONSENT FORM.

CONSENT FORM

TITLE OF RESEARCH: Evaluation of the Safety and Efficacy of Trimycin vs. Hydrochlorothiazide in the Treatment of Hypertension

IRB PROTOCOL: F##########

INVESTIGATOR: John Doe, Ph.D.

SPONSOR: If the protocol is being sponsored by UAB departmental funds or is unfunded, put the name of the department here (e.g., UAB Department of Medicine). For student research, include the student's departmental affiliation.

If additional or other support is being provided, include this information with a heading such as "**SUPPORTED BY:**" After the SPONSOR line.

SPONSOR: Wise Drug Company, Inc.

RESEARCH INVOLVING CHILDREN:

- When a parent or guardian is providing consent for only the child participant who will sign the assent section of the consent form, do not use "you/your child" throughout the form. Instead, use "you" and insert the following text after the SPONSOR line and before the Purpose of the Research section:

For Children (persons under 19 years of age) participating in this study, the term "You" addresses both the participant ("you") and the parent or legally authorized representative ("your child").

- When a parent or guardian is providing consent for only the child participant who will sign a separate assent form or who will not provide written assent, use "your child" throughout the form.
- When a parent or guardian is providing consent for both him/herself and the child participant, specify throughout the consent form when you are referring to the parent and when you are referring to the child. This would allow for the use of "you," "your child," and "you and your child" throughout the form.

Purpose of the Research

- Explain the purpose of the study in nontechnical language.
- Describe why the participant is being asked to join.
- State that the study involves research.
- If drugs or devices are used, indicate whether they are FDA approved or investigational.
- If applicable, explain what a Pilot, Phase I, II, III, or IV drug study is.
- State the total planned number of participants (e.g., individuals, records, specimens) to be enrolled by the UAB investigator, and studywide for multicenter studies.

We are asking you to take part in a research study. This research study will test how well a new drug lowers blood pressure. The new drug, Trimycin, is investigational and not yet approved by the U.S. Food and Drug Administration (FDA). People who enter into the study will take either the new drug, Trimycin, or Hydrochlorothiazide (water pill). Hydrochlorothiazide is the FDA approved drug that most people take now to lower blood pressure. Trimycin is approved in Europe, but has not been approved in the United States. More than 200 people in other research studies in the United States have safely used Trimycin. This is a Phase III study. A Phase III study is a research study that looks at a large number of patients receiving a common or routine treatment. This study will enroll 200 participants nationwide, and 20 of them will come from UAB.

Explanation of Procedures

- Describe the procedures to be followed, identifying which procedures are for research and which procedures are standard of care.
- Identify which procedures are experimental.
- Estimate the amount of time involved in study participation.
- If specimens (e.g., blood, tissue, body fluids) will be collected as part of the research procedures, describe the collection in this section. If the specimens will be stored for future research, describe the storage procedures under "Storage of Specimens for Future Use."

If you enter the study, all your current blood pressure medicines will be stopped for 1 month. During this time, you will be given pills called placebos. A placebo does not have any active medicine, so it should not have any effect on your blood pressure. However, this placebo might cause your blood pressure to lower. The study staff will need to watch your blood pressure closely while you are not on any medicine for your blood pressure. Your blood pressure will be watched to make sure it does not rise so high that you need immediate treatment. You will need to come for office visits three times during the first week. You will need to come for office visits two times per week during Weeks 2, 3, and 4. If your blood pressure is in the range required after Week 4, you will be entered into the study. If your blood pressure is not in the range required after Week 4, you will not be entered into the study and will receive standard care for your blood pressure. If you are entered and complete the entire study, you will be in the study for 6 months. If you qualify for the study, you will be randomly picked (like the flip of a coin) by a computer to receive either Trimycin or Hydrochlorothiazide. You will take the medicine once a day by mouth. This will be a double-blind study. This means neither you nor your doctors will know which medicine you are taking. If medically necessary, the doctor can find out which drug you are taking.

These tests will be made during the study: lab blood tests, urine tests, weight measures, resting electrocardiogram, heart rate, and blood pressure. (An electrocardiogram measures the electrical activity of the heart.) You will be asked to come back to the clinic for 20 weekly visits. At each visit you will be asked if you have had any bad reactions and how you are feeling on the drug.

If drug screening is part of the protocol, include a statement such as:

If you have used any illicit (street) drug(s) within the past 3 months, we ask that you not participate in this project.

Where HIV testing is conducted, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling before and after the testing.

Where other protocol testing for reportable diseases is conducted, individuals will be informed of the results and told where to obtain counseling and referred to their primary care physician or the state health department.

Incidental Findings

If research-only imaging studies are part of the protocol, address whether or not the images will be read for incidental findings. If the images will not be read for incidental findings, include the following:

We are performing imaging solely for the research purposes described above. It is not a clinical scan intended for diagnostic or therapeutic purposes. Under no circumstance will the investigator, research staff, or imaging staff interpret the scan as normal or abnormal. They are unable to make any medical comments about your scan. The scan will not be looked at or read for any healthcare treatment or diagnostic purpose. If you want your scan to be reviewed by a physician so that the physician can look for medical issues, you can request a copy of your scan. We will provide an electronic copy at no charge.

Risks and Discomforts

- Include any foreseeable risks or discomforts to the participant (e.g., physical, social, financial, loss of employability, reputation, and breach of confidentiality).
- When possible, quantify the risks involved (e.g., *common*, *rare*, percentages).
- If the study involves a placebo,
    - define placebo (not as *treatment* or *medication*; see paragraph above that begins "*If you enter the study...*")
    - describe what complications may result
    - describe the precautions that will be taken to protect the participant during this time.
- Do not include risks or discomforts associated with drugs or interventions that are not being administered or performed as part of this study.

You may have some side effects from taking these drugs. The side effects of Trimycin are headaches, feeling drowsy, and feeling tired. About forty percent (40%) of people who take Trimycin have reported feeling drowsy and tired. About twenty percent (20%) of people who take Trimycin have headaches. Hydrochlorothiazide can cause the following side effects: low blood potassium; a rise in blood uric acid and blood sugar; and a lowering of red and white blood cells. About eighty percent (80%) of people who take Hydrochlorothiazide have these problems. There may also be risks that are unknown at this time. You will be given more information if other risks are found.

Randomization: If your protocol involves randomization, include a paragraph on risks of randomization. Ensure the risks of all study arms are described in detail in this section, even if the procedures in those arms would be standard of care if the participant was not in the study. For example:

You will be assigned to a treatment group by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

Information for Women of Childbearing Potential and/or Men Capable of Fathering a Child

If applicable, include this section and address the precautions that should be taken by women of childbearing potential and/or by men capable of fathering a child before, during, and/or after participation. List the specific acceptable methods of birth control for participants involved in the study. Use only the information that is applicable to the study population.

We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time Women who can become pregnant must take a pregnancy test before the start of the study.

You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex.

Unless you cannot have children because of surgery or other medical reasons, you must have been using an effective form of birth control before you start the study. You must also agree to continue to use an effective form of birth control for 6 months after taking the study drug. Effective birth control includes birth control pills, patch, IUD, condom, sponge, diaphragm with spermicide, or avoiding sexual activity that could cause you to become pregnant.

Benefits

- State any potential benefits to the participant or to others that may reasonably be expected from the research.
- Do not overstate benefits.
- If there is no potential for direct benefit to the participant, that should also be stated.
- **Do not include** medication, treatment, devices, or compensation information.

You may not benefit directly from taking part in this study. However, this study may help us better understand how to treat high blood pressure in the future.

Alternatives

- Include appropriate alternative procedures or courses of treatment that may be advantageous to the participant.

- One alternative may be to not participate in the study.

There are many other drugs that are used to treat high blood pressure. Some examples of these drugs are Betasan, Enapror, and Ditserin. The investigator or research staff will discuss these other drugs with you.

Confidentiality

- Include information regarding anyone who will receive identifiable data (e.g., through subcontracts or other agreements.
- Include the US Food and Drug Administration (FDA) if the research involves a drug, device, or biologic subject to FDA oversight.

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of [ADD SPONSOR NAME] and the Office for Human Research Protections (OHRP). The results of the treatment may be published for scientific purposes. These results could include your [ONLY INCLUDE APPLICABLE] lab tests and X-rays. However, your identity will not be given out.

Permanent Medical Record: If the consent form will be placed in the participant's permanent medical record at University of Alabama Hospital and/or The Children's Hospital of Alabama, include the following:

If any part of this study takes place at

[UAB ONLY] University of Alabama Hospital
[TCHA ONLY] The Children's Hospital of Alabama
[UAB & TCHA] University of Alabama Hospital and The Children's Hospital of Alabama

this consent document will be placed in your file at that facility. The document will become part of your medical record chart.

Billing Compliance Language: Only if "clinical billable services" will be provided at a UAB Health System location (i.e. HSF Clinics, UAB Hospital, UAB Highlands, or Callahan Eye Foundation) or The Children's Hospital of Alabama, include the language below, as applicable. If you have questions about UAB's clinical trial billing, contact the Fiscal Approval Process (FAP) staff at FAP@uab.edu. For details on submission requirements, go to http://www.uab.edu/osp/fiscal-approval-process-fap. If you have questions about clinical trial billing for studies conducted at The Children's Hospital of Alabama, contact Pam Barlow at pam.barlow@chsys.org or 558-2452.

Information relating to this study, including your name, medical record number, date of birth and social security number, may be shared with the billing offices of

[UAB ONLY] UAB and UAB Health System affiliated entities
[TCHA ONLY] The Children's Hospital of Alabama and its billing agents

[UAB & TCHA] UAB and UAB Health System affiliated entities, along with The Children's Hospital of Alabama and its billing agents

so that claims may be appropriately submitted to the study sponsor or to your insurance company for clinical services and procedures provided to you during the course of this study.

International Protocols: Only if the study is conducted outside the United States or sponsored by a company based outside the United States and foreign regulatory agencies will have access to identifiable research records, include the following:

Monitors, auditors, the Institutional Review Board for Human Use, and regulatory authorities will be granted direct access to your original medical records for verification of trial procedures and/or data without violating confidentiality.

ClinicalTrials.gov: For applicable clinical trials, include the statement below. It is the responsibility of the sponsors and investigators to determine if their clinical trial meets the definition of an "applicable clinical trial" and to ensure compliance with the most current applicable statutory and regulatory requirements. If you have any questions regarding registering a study on ClinicalTrials.gov, contact Penny Jester at 934-2424 or pjester@uab.edu.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Reportable Diseases/Conditions: Only if the investigator will be testing for any reportable diseases/conditions, include a statement specifying what reportable diseases/conditions are being tested and that positive results will be reported to the county or state health department.

Screening for Drugs, Observations of Abusive Behavior: Only if the investigator will conduct drug screening or inquire about abusive behavior (e.g., child or elder abuse or neglect, or harm to self) as part of the protocol, include the following statement:

Information obtained during the course of the study which, in the opinion of the investigator(s), suggests that you may be at significant risk of harm to yourself or others will be reportable to a third party in the interest of protecting the rights and welfare of those at potential risk.

Genetic Research: Only if the research involves genetic testing, describe the protections provided to the participant under GINA. For questions regarding GINA, see the IRB Guidebook. The following may be used for the description:

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

Voluntary Participation and Withdrawal

- Include the consequences of a participant's decision to withdraw from the research.
- Include procedures for orderly termination of participation by the participant.
- If applicable, include anticipated circumstances under which the PI without regard to the participant's consent may terminate the participant's participation (see second paragraph below).

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care.

You may be removed from the study without your consent if the sponsor ends the study, if the study drug is approved by the FDA, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

If students or employees of UAB may participate in the study, the IRB recommends using the following language in the consent form:

If you are a UAB student or employee, taking part in this research is not a part of your UAB class work or duties. You can refuse to enroll, or withdraw after enrolling at any time before the study is over, with no effect on your class standing, grades, or job at UAB. You will not be offered or receive any special consideration if you take part in this research.

Cost of Participation

- If any costs to the participant or the participant's health insurance might result from the research (e.g., for tests, drugs, biologics, devices, or copayments), describe those costs. Include information about any financial assistance that may be available, such as how to consult a social worker.
- If there is no cost to the participant, this should be stated.

There will be no cost to you for taking part in this study. All drugs, exams, and medical care related to this study will be provided to you at no cost during the 6-month study period.

If standard medical care may be provided during the study include the following statement:

The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

If participants may be enrolled in Medicare Advantage and will have study related services billed to their Medicare Advantage insurance, include the following statement. If you have questions regarding the inclusion of this statement, contact the Fiscal Approval Process (FAP) staff at FAP@uab.edu.

If you are in Medicare Advantage (Medicare managed care plan), you should contact someone at your plan before you start a clinical trial. They can provide more information about additional costs you could incur from participating in clinical trials.

Payment for Participation in Research

- Note: Payment may not be based upon successful completion of the protocol.
- Specify the amount and type/method of compensation a participant will receive for participating OR that there is no compensation for participation.
- If applicable, include the payment schedule.
- Describe prorated payments for participants who withdraw before the end of the study.
- If children are involved, specify whether the child or parent is being paid.

You will be paid $10 for each study visit, including the placebo phase of the study. If you quit the study, you will be paid $10 for each study visit made to the clinic. Payments will be made after 3 months and 6 months if you complete the entire study. Payments will be made by check sent to you in the mail. If you do not finish the entire study, you will be paid at the time you decide to stop taking part in the study. If you complete the entire study, you will receive a total of $290.

If a participant is to earn $600 or more in a calendar year from their participation in research, include the following language:

You are responsible for paying any state, federal, Social Security or other taxes on the payments you receive. You will receive a form 1099 in January of the year following your participation in this study. This form is also sent to the IRS to report any money paid to you. No taxes are kept from your check.

Payment for Research-Related Injuries

- Include this section only if the research involves (a) greater than minimal risk or (b) procedures or interventions that could result in harm or injury.
- If the section is to be included, include the UAB statement below.

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

In addition, if the research is sponsored, include language that addresses whether or not the sponsor(s) will provide compensation for research-related injuries.

- For sponsored research where the sponsor(s) **will not** pay for compensation to injured research participants or pay for medical treatment of research-related injuries, list the names of all sponsors after "UAB".

UAB and Wise Drug Company, Inc. have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

- For sponsored research where the sponsor(s) **will** pay participants for either compensation or treatment for research-related injuries, include the specific language provided by the sponsor(s) regarding injury compensation. The IRB must be provided with "sponsor verification" either in the form of a letter signed by the sponsor(s) with the same wording given in the consent form or a model consent form included in the protocol and listed in the Table of Contents of the protocol with the same wording. Do not submit a copy of the indemnification letter as the verification. Include information regarding what medical treatment will consist of if injury occurs and where further information may be obtained.

Significant New Findings

Indicate that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided to the participant by the principal investigator or his/her staff.

You will be told by your doctor or the study staff if new information becomes available that might affect your choice to stay in the study.

Genome-Wide Association Studies (GWAS)

For protocols that are considered Genome-Wide Association Studies (GWAS), UAB must certify that plans for the submission of genotype and phenotype data from GWAS to the NIH meet the expectations of the policy. See the IRB Guidebook for more information on what should be submitted for this certification. For applicable protocol, include the following:

The DNA that composes your genes will be analyzed and that data, which is referred to as your genotype or complete genetic makeup, will be compared to your phenotype, which consists of your observable traits, characteristics, and diseases. Your genotype and phenotype data will be shared for research purposes through the National Institutes of Health (NIH) Genome-Wide Association Studies (GWAS) data repository. The aim of this research is to discover genetic factors that contribute to the development, progression, or therapy for a particular disease or trait.

Questions

- Include the name of the Principal Investigator and his/her contact number for participants to contact regarding the research and research-related injuries.
- Include the names of additional contact personnel, if applicable.

If you have any questions, concerns, or complaints about the research or a research- related injury including available treatments, you may contact Dr. John Doe. He will be glad to answer any of your questions. Dr. Doe's number is 205-934-3810. Dr. Doe may also be reached after hours by paging him at 205-934-3411 (beeper 9999).

Include for the Office of the IRB contact information.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Storage of Specimens for Future Use

If specimens (e.g., blood, tissue) obtained for the research may be stored for research not specifically defined in the protocol, place this section after Legal Rights and before Signatures. At a minimum, address the following points and include lines for participants to initial (do not use checkboxes):

- What kind of specimens will be collected and the means of collection.
- What type of research will be done with the specimens.
- Whether the specimens will be shared with other investigators
- Whether the specimens will be coded or anonymized (no way of tracing back to participant/uncoded or code destroyed).
- Whether the participant may be contacted for additional consent.
- How long, if known, the biological specimens will be stored. (Short- term: current protocol only or other current research; Long-term: future studies on disease or condition, repository, etc.).
- Foreseeable risks or benefits to participants in the collection, storage, and subsequent research use of specimens.
- What will be done with the biological specimens if the participant refuses permission.
- What will be done with the research results. (Research results should not be placed in the individual participant's medical record.)
- Potential for commercial use of the subject's specimen(s).
- How to withdraw consent for future use.

As part of this study, we would like to store some of the blood and urine specimens collected from you for future research on hypertension. The future research may be conducted by Dr. John Doe or by other researchers that obtain IRB approval for their research. The specimens will be

labeled with a code that only Dr. John Doe can link back to you. Results of any future research will not be given to you or your doctor. The specimens obtained from you in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to you should this occur.

You do not have to agree to allow your blood and urine specimens to be stored in order to be part of this study.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact Dr. John Doe at the University of Alabama at Birmingham at 205-934-3810. Once the request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

Initial your choice below:

___ I agree to allow my samples to be kept and used for future research on hypertension.

___ I do not agree to allow my samples to be kept and used for future research.

Signatures

It is impossible to address all scenarios for signature requirements that may be needed for various types of research. These instructions and samples are designed to assist you in the preparation of the Signatures section. In many cases, the Signatures section will need to be customized for the particular study population.

- The requirements for signature lines depend upon the consent process described in the Human Subjects Protocol.
- Each signature-date line included in the Signatures section, as applicable to the research, must be signed and dated.
- All signatures must appear on the same page, but that page does not need to be a separate page with no other information.
- Each person who signs the consent form must include the date of his/her signature.
- If the research involves children (i.e., individuals younger than 19 years of age for research conducted in the state of Alabama), see "Children" under General Information in the IRB Guidebook and see Example Signatures for Research Involving Children, below.
- If the research involves pregnant women. see "Pregnant Women, Fetuses, Neonates" under General Information in the IRB Guidebook.
- A signature-date line for the participant must be included. The three acceptable options are shown and described below.

Your signature below indicates you agree to participate in this study. You will receive a copy of this signed consent form.

Option 1

Signature of Participant Date

Option 2

Signature of Participant or Legally Authorized Representative Date

Option 3

Signature of Participant Date

Signature of Legally Authorized Representative Date

Legally Authorized Representatives (LAR)

- If the research proposes to obtain consent from the participant **or** the LAR, add "(or Legally Authorized Representative)" after "Signature of Participant."
- If the research proposes to obtain consent from the participant **and** the LAR, include a separate signature-date line for each person.
- If an individual is not capable of providing informed consent, the IRB allows that it may be obtained from the individuals listed below in priority order:
    - Judicially appointed guardian or individual named in a durable power of attorney;
    - Spouse;
    - Sons or daughters 19 years of age or older;
    - Either parent;
    - Brother or Sister 19 years of age or older;
    - Other nearest kin 19 years of age or older.

Signature of Principal Investigator Date

- All persons who discuss or obtain informed consent must be listed in the HSP.
- If the principal investigator is not the only person who will conduct informed consent discussions and obtain signatures, add "or Other Person Obtaining Consent" after "Signature of Principal Investigator."
- If the Principal Investigator will never obtain informed consent, this signature-date line should be labeled "Signature of Person Obtaining Informed Consent."

Signature of Witness Date

- Include this line unless the PI requests and justifies, and the IRB approves a waiver of the witness requirement.
- The person administering the consent (e.g., study coordinator) cannot sign as the witness.

Reviewed by:

Signature of Principal Investigator Reviewing Consent Document Date

Include this line **only if** the HSP specifies that the principal investigator will not obtain informed consent but will only review signed consent documents.

Signatures for Research Involving Children

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to allow your child to participate.

- The requirements for signature lines depend upon the consent process described in the Human Subjects Protocol. See the instructions and options below.
- The UAB IRB usually recommends the following:
  - Waiver of assent needs to be documented for participants under 7 years of age, but these participants should be included in the consent process if possible.
  - A separate assent form should be prepared for use with, and to document the assent of, participants who are 7-13 years old.
  - Participants 14-18 years old document their assent by signing the main consent form.
- If the IRB determines the permission of only one parent or guardian is necessary, only include one line for "Signature of Parent or Guardian" below.
- A parent, for purposes of consent, means either a child's biological or adoptive parent. In some instances, the consent of a guardian may be used in lieu of parental consent. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. For purposes of research conducted in Alabama a *guardian* is:
  1. A person appointed guardian of a child pursuant to the Alabama Uniform Guardianship and Protective Proceedings Act (Code of Alabama, Title 26) as documented by a valid court order;
  2. A person having legal custody of a child and as documented by court order;
  3. A person acting *in loco parentis*, regardless of whether such is documented by a court order. A person acts *in loco parentis* of a child where the individual voluntarily assumes responsibility for the child's custody, care, and maintenance even though no court order exists formally appointing the person as the guardian, legal custodian, or adoptive parent of the child. If such individuals may provide permission for the enrollment of children, the Human Subjects Protocol must explain how the investigator will confirm the *in loco parentis* relationship.

You will receive a copy of this signed informed consent document.

Signature of Participant 14-18 Years of Age Date

Signature of Parent or Guardian Date

Signature of Parent or Guardian Date

Signature of Investigator or Person Obtaining Consent Date

Signature of Witness Date

If the assent of any child participant may be waived, include the following section with the applicable reason(s) for waiver of assent marked:

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____ Maturity _____ Psychological state of the child _____

Signature of Parent or Guardian Date

Signature of Parent or Guardian Date

Signature of Investigator or Person Obtaining Consent Date

Signature of Witness Date

University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant Name: _____
Research Protocol: Evaluation of the Safety and Efficacy of Trimycin vs. Hydrochlorothiazide in the Treatment of Hypertension

UAB IRB Protocol Number: F##########
Principal Investigator: John Doe, Ph.D.

Sponsor: Wise Drug Company, Inc.

What health information do the researchers want to use? All medical information and personal identifiers, including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date: _____

or participant's legally authorized representative: _____ Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____

Appendix II – New Protocol Checklist

New Protocol Checklist

☐ Full Convened ☐ Research no more than minimal risk (Expedited Category #_____)

Principal Investigator: _____ FAX: _____ IRB Protocol #: _____

Contact Person: _____ PHONE: _____ ☐ *IRAP Created*

Protocol Title: _____

Faculty Sponsor: _____ Training Complete: Y N - Needed for: _____

Sponsor: _____ ☐ DOD ☐ DOE ☐ DE ☐ DOJ/NIJ/Bureau of Prisons ☐ ICH/GCP applies

OSP Proposal # _____ ☐ Funding App/Grant ☐ Subcontract ☐ MTA ☐ CDA ☐ DUA ☐ FFS

☐ HSP	☐ Sponsor Protocol (date) _____	
☐ PORF or CTRC	☐ Titles Match – ☐ Grant/Sponsor Protocol ☐ HSP ☐ ICF	
☐ 1572	☐ IB, Package Insert, or Device Manual _____	
☐ Waiver of IC	☐ Waiver of Auth & IC	☐ Waiver of IC Documentation
☐ Consent/Assent Form(s) # _____	☐ Sponsor Sample CF	☐ ICH/GCP criteria met (if applicable)

☐ Title, IRB Protocol #, Investigator, & Sponsor/Support	☐ Alternatives	☐ Payment for Participation
	☐ Confidentiality	☐ UAB Injury Statement
☐ Version Date	☐ Permanent Medical Record	☐ Sponsor Injury Statement
☐ Page #s	☐ UAB ☐ TCHA	☐ Sponsor Verification
☐ You/your child box	☐ Billing Compliance	☐ New Findings
☐ Purposes of the Research	☐ UAB ☐ TCHA	☐ GWAS
☐ Statement re: research	☐ International Protocol	☐ Name/Number (Research/Injury)
☐ Explanation of Procedures	☐ Clinical Trials.gov	☐ Name/Number (Participant Rights)
☐ Identify experimental procedures	☐ Reportable Diseases/Conditions	☐ Legal Rights
☐ Expected duration of participation	☐ Screen Drugs/Observe Abuse Behavior	☐ Storage of Specimens
☐ Incidental Findings	☐ Genetic Research/GINA	☐ Signatures
☐ Risks and Discomforts	☐ Voluntary Participation & Withdrawal	☐ Assent of Child/Waiver of Assent
☐ Randomization risks	☐ Student/Employees	☐ HIPAA
☐ Childbearing &/or Fathering	☐ Cost of Participation	
☐ Benefits	☐ Cost of SMC	☐ FAP
	☐ Medicare Advantage language	

☐ Pharmacy Release	☐ TKC, notif attached - Y N
☐ Radiation Safety Approval	☐ UH, notif attached - Y N
☐ Infection Control Approval	☐ UAB Highlands, notif attached - Y N
☐ Pathology Release	☐ TCHA, notif attached - Y N
☐ IBC Approval	☐ EFH, notif attached - Y N
☐ CIRB Conflict Identified	☐ CRU, notification attached - Y N
☐ Include CIRB Language	☐ Other UAB sites _____
☐ FERPA Applies	☐ Non UAB sites _____
☐ PPRA Applies	Engaged in Research: Y N If yes, IRB approvals Y N

☐ Children - CRL# ____ ☐ Pregnant Women & Fetuses ☐ Nonviable or UV Neonates ☐ Decisionally Impaired

☐ Prisoners - Cat# ____ ☐ Student/Employees ☐ Non-English Speakers

☐ Recruitment Materials _____ ☐ Partial Waiver of Authorization

☐ SAE Log submitted. Date/numbers _____ ☐ Screening Script/Questionnaire

☐ Other Questionnaires _____

Phase: _____ ☐ DSMB ☐ Int. Analysis ☐ Sponsor/PI Monitoring Plan ☐ Plan Described

☐ Describes alternate plan for SAE reporting ☐ Board approved at meeting?

☐ Requests waiver of 24 hour "think it over" ☐ Board approved at meeting?

Drugs/Devices Name and IND/IDE Number

☐ IRB pre-start up visit taken place, if Investigator is both sponsor and holder of IND/IDE ☐ *IRAP Approved*

WRITE REVIEWER NOTES ON BACK OF THIS PAGE.

*Memo Faxed*_____ *Mailed*_____ *Approval Form Mailed*_____ *Follow-Up Letter*_____