Webinar Series

Peeling Back the Layers of a Waiver of Informed Consent

August 26, 2015

Presented by:
Rebecca Ballard, JD, MA, CIP
Vice President of Compliance & Board Operations
About Schulman Associates IRB

- Established in 1983
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full board meetings five days a week
- Dedicated daily expedited review of qualifying minimal risk protocols
About Schulman Associates IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- **Phase I Board** with streamlined processes tailored to Phase I timelines
- **Oncology Review Board** for all phases of oncology research
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

Provision is a joint venture between Schulman Associates IRB and Falcon Consulting Group
About Today’s Presenter

Rebecca Ballard, JD, MA, CIP
Vice President of Compliance & Board Operations

- JD and MA in Bioethics from Indiana University School of Law, Indianapolis
- Previously Director of the Office of Research Integrity at Children’s Mercy Hospitals & Clinics
  - Responsible for Pediatric IRB administrative operations and primary resource for investigators regarding IRB issues
- Also served as Research Compliance Officer (RCO) for the Department of Veteran Affairs
  - Developed Research Compliance Program at the Kansas City VAMC
Today’s Goal
Objectives

- Review the criteria to waive informed consent.
  - Focus on the criteria: “Research could not practicably be carried out without the waiver or alteration.”

- Analyze common investigator justifications for the practicability criteria.

- Develop a deeper understanding on when research could not practicably be carried out without the waiver.
Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

45 CFR 46.116

21 CFR 50.20
Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.
## Peeling Back a Layer — DHHS v. FDA

<table>
<thead>
<tr>
<th>DHHS 45 CFR 45.116</th>
<th>FDA 21 CFR 50.20</th>
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| Waiver of consent process possible under 45 CFR 46.116(d). | No waiver of consent unless the clinical investigation certify in writing all of the following:  
1. The human subject is confronted by a life-threatening situation necessitating the use of the test article.  
2. Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.  
3. Time is not sufficient to obtain consent from the subject's legal representative.  
4. There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. | 21 CFR 50.23 |
|                     | No waiver of consent unless conducting emergency research under 21 CFR 50.24. |
Waiver of Informed Consent

➢ Research involves no more than minimal risk to subjects
➢ Waiver/alternation will not adversely affect rights and welfare of subjects
➢ Research could not practicably be carried out without the waiver or alteration
➢ Whenever appropriate, subjects will be provided pertinent information after participation

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45 CFR 46.116(d)
It’s Only a Retrospective Review
“This is a retrospective chart review only with no more than minimal risk.”

“This is a retrospective chart review only, involving no interaction or intervention with participants.”
IRB approved a waiver of the requirement for informed consent for all research involving retrospective review of medical records.

OHRP finds that the IRB failed to document the specific criteria for waiver of informed consent for the research.

## Not All Retrospective Studies Are Alike

| 1. A retrospective review of medical records from patients currently seen regularly in clinic |
| 2. A retrospective review of a few records |

| 3. A retrospective review of medical records from patients seen years ago |
| 4. A retrospective review of thousands of records |
Factors That May Help Determine If Impracticable

- Is contact information of potential subjects readily available?
- Are potential subjects likely to be expired?
- Number of records required to review
- Age of records
It’s Only Minimal Risk
“It would not be practical to obtain signed consent from the research subjects, and because the study would cause no more than minimal risk, it would not benefit the patient to pursue consent.”

“Since there is minimal risk, and this is an observational study it would be rather pointless to obtain consent.”
The IRB found the research presented no more than minimal risk but OHRP found no documentation that the IRB made the three additional requirements at 45 CFR 46.116(d).

OHRP, Letter to Dr. Norman Altman from Sandford Leikin, MD (1/19/2001)
IRB Responsibilities: Gotta Go through the Paces

➢ "OHRP found no evidence the IRB satisfied the requirement to find and document specific criteria when approving a waiver of informed consent.” OHRP, Letter to Mary Beth Burns from Kristina Borror (12/13/2002)

➢ "OHRP finds no evidence IRB made and documented the findings to waive informed consent.” OHRP, Letter to Kenneth L. Dretchen from Kristina Borror (10/4/2000)

➢ “IRB granted a waiver of informed consent but the IRB approval for waiver was not adequately documented by the IRB in either the minutes or approval letter.” OHRP, Letter to Bruce Wellman, MD from Lisa A. Rooney, JD (12/16/2009)
The IRB strengthened its documentation requirements by providing more explicit statement of criteria in which decisions are made.” — OHRP, Letter to Mary Beth Burns from Kristina Borror (12/13/2002)

Need to explicitly state that the IRB found each and every criteria for the waiver are met.
Subjects Are Not in Front of Me
“It is not practicable to conduct research without the waiver as there is no actual patient participation or involvement in this study.”

“This study involves no subject contact or intervention.”
Case Study

Children, ages 3 – 17, who presented in the emergency dept. from July – Dec with signs suggestive of acute appendicitis were prospectively identified

- Unequivocal clinical presentations for appendicitis
  - Appendectomy w/o Imaging studies

- No symptoms for appendicitis
  - Discharged home w/o imaging studies

- Equivocal clinical findings
  - Study cohort: Pelvic Ultrasonography
    - Ultrasonography = ? appendicitis
    - Ultrasonography = appendicitis
      - Laparotomy performed
Case Study

- Children and adolescents presenting in ER from July to December 1998, with signs suggestive of acute appendicitis, were prospectively identified.

Would you find the waiver criteria met?
- Yes
- No
“[I]t appears that it would have been practicable to obtain parental permission for at least the conduct of the follow-up research interviews and probably for the prospective collection of routine clinical data related to the emergency room evaluation. If so, the research would have not have satisfied the requirements for waiver of informed consent.”

OHRP, Letter to William New from Patrick J. McNeilly, PhD (2/8/2001)
Not Enough Space
The investigator claimed there was not enough space in the magazine where he wanted to advertise the study to present the informed consent information.
The PI stated that space limitations of the magazines in which some of the surveys were printed prohibited him from including all the elements of informed consent.

OHRP found the IRB approved a version of the survey/informed consent required by DOD which included many more of the required elements of informed consent.

OHRP, Letter to Mary Beth Burnside, Ph.D. from Kristina C. Borror, Ph.D. 12/3/2002
OHRP concluded, “It is difficult to see how the other surveys would have been impracticable to carry out by including these and other required elements, particularly for the web-based version of the questionnaire, as well as questionnaires that were mailed to subjects, which did not have the same space restraints as those printed in magazines.”

OHRP, Letter to Mary Beth Burnside, Ph.D. from Kristina C. Borror, Ph.D. 12/3/2002
It's Just Too Hard to Get Informed Consent
“Requiring informed consent will slow down the process, and in some cases may skew survival rates shown by data.”

“It would take longer for the subjects to complete the informed consent process than it would to complete the survey....”
“[N]ote that mere inconvenience in contacting individuals is not a justification for concluding that obtaining informed consent is impracticable.”

OHRP, Letter to Dr. Gerald Litwack from Carol J. Weil, JD (6/10/2002)

See also OHRP, Letter to Dr. Fazwaz T. Ulaby from Carol J. Weil, JD (04/29/2002)
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What about Clinic Interference?
“Subjects who are currently or will be in the future patients and be a part of this study are numerous and it may interfere with clinic to secure signed informed consent.”

“Requiring informed consent will slow down the process, and in some cases may skew survival rates shown by data.”

“It would take longer to complete the informed consent process than it would to complete the survey, and in the busy working environment, it is unlikely that they would be willing to participate.

Would you accept clinic interference as an excuse to find consent not practicable?

- Yes
- No
The burden of the researcher to the IRB is to meet the benchmark of the word ‘practically’ requires more than mere inconvenience. That is, the researcher must provide substantial evidence that not waiving the consent form will be intrusive (well beyond “slowing down the process”) and add confounding bias to the research such as delaying immediate needed health care thus placing subjects in health crisis. To add a consent form to a package of forms the subject is already completing to receive health care does NOT meet this benchmark.

Email from Alfredo R. Sancho, PhD, MPH, Commander, U.S. Public Health Services to Rebecca Ballard (8/13/2015) (emphasis added in red)
What About Costs?
“The large number of patients needed to conduct this research prohibits the collection of consent, as such a requirement would place undue cost and burden on the research team and would render the research unfeasible.”

“A prospective pilot study screening hundreds of subjects would be cost-prohibitive.”
“If the study involves review of, say medical records, then it may be impracticable to do the research if consent is required. If the study involves a survey, or interview, then it is not clear that it would meet the practicability requirement.”

Email from Kristina C. Borror, Ph.D., Director, OHRP to Rebecca Ballard (8/17/2015)
Getting Informed Consent Will Lower My Enrollment Numbers
“We believe that contacting patients via phone or letter in order to obtain informed consent is not practicable. Taking this approach may lead to a low participation rate, which will bias the data and invalidate our findings. If some patients who present to the clinic refuse to give consent, then this could also introduce bias.”
Study team claimed subject enrollment is too low when informed consent is solicited with a procedure that required all elements of informed consent.

OHRP, Letter to Eugene P. Trani, PhD from Micheale Carome, MD (9/22/2000)
OHRP is concerned that the justification proposed by the investigator for finding that the research could not practicably be carried out without the waiver ... is not ethically justifiable.”

“In specific, claiming that subject enrollment is too low when informed consent is solicited with a procedure that includes all required elements of informed consent stipulated by HHS regulations at 45 CFR 46.116 would not be an acceptable justification for the waiver.”

OHRP, Letter to Eugene P. Trani, PhD from Micheale Carome, MD (9/22/2000)
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“In specific, claiming that subject enrollment is too low when informed consent is solicited with a procedure that includes all required elements of informed consent stipulated by HHS regulations at 45 CFR 46.116 would not be an acceptable justification for the waiver.”

OHRP, Letter to Eugene P. Trani, PhD from Micheale Carome, MD (9/22/2000)
Let’s Recap
# Conclusion

## #5: It’s only Minimal Risk

Don’t fall into the trap of collapsing the practicability criteria into the minimal risk criteria.

## #4: Subjects are not in front of me

May be practicable to obtain consent for at least a part of the study, such as follow-up interviews.

## #3: Not Enough Space

If more than one way to present consent info that does not have same space restrictions, then not impractical.

## #2: Just too hard

‘Practically’ requires more than mere inconvenience. Researcher must provide substantial evidence that not waiving consent will be intrusive (well beyond “slowing down the process”) and add confounding bias to the research such as delaying immediate needed health care thus placing subjects in health crisis.

## #1: Lowers Enrollment #s

Claiming that subject enrollment is too low when informed consent is solicited is not ethically justifiable.
“OHRP recommends that when approving the waiver the IRB ensures that research could not practically be carried out without the waiver.” OHRP, Letter to Mary Beth Burns from Kristina Borror (12/3/2002)

“That said, we have given great deference to the IRB in making its decision regarding whether a specific set of facts meets the "impracticability" criteria.” Email from Kristina C. Borror, Ph.D., Director, OHRP to Rebecca Ballard (8/17/2015)
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