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
About Schulman Associates IRB

- Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

www.provisionrcs.com

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

Rob Romanchuk, BSHS, CIP, CCRC, CHRC, CCRCP
IRB Vice Chairperson

- BSHS, Clinical Research Administration, The George Washington University
- Extensive experience in IRB and research operations, HSP and GCP auditing and training
- ACRP chapter chair 2011-2014
- Frequent presenter at ACRP, MAGI and other venues
Objectives

- Discuss regulations governing HUDs
  - Distinguish from IDE regulations
- Review current FDA guidance on IRB review of HUDs
- Consider challenges facing institutions and IRBs in the use of HUDs
- Provide workable solutions
Humanitarian Use Device – HUD

Intended to benefit patients in treatment and diagnosis of disease or conditions that affect or is manifested in fewer than 4,000 individuals in the US per year

Office of Orphan Products Development determines HUD status

Governed by 21 CFR 814.100

- HUD regulations
HUD – Road to Approval

- Holder first requests an HUD designation for the device from the Office of Orphan Products Development (OOPD)
- Once granted, may apply for an HDE – Humanitarian Device Exemption
  - Exempt from requirement to demonstrate assurance of effectiveness otherwise required for medical devices
Must demonstrate that:

- HUD does not pose unreasonable risk of injury to patients
- That the probable benefits outweigh risk of injury from use

Label includes:

- The device is a HUD
- Is authorized to treat or diagnose a specific disease or condition
- Effectiveness has not been demonstrated
HDE Holder Responsibilities

- Have approvals before shipping
- Ship only to institutions with IRB oversight
- Ensure initial and continuing IRB review
- Assure no use prior to IRB approval
- Maintain IRB correspondence
- Submit annual reports to FDA including safety events
IDE/HUD Important Differences

- **Acronym**
  - Investigational Device Exemption: exemption allows sponsor to ship investigational (aka unapproved) device
  - Humanitarian Device Exemption: exemption from effectiveness requirements imposed on IDEs
    - Once granted, is now an approved device (not investigational)—allows HUD to be marketed

- Not subject to IDE regulations
IDE/HUD Differences – Road to Approval

- **PMA**
  - Approved based on valid scientific evidence and reasonable assurance that the device is safe and effective for its intended use

- **510K**
  - Approved because it is judged at least as safe and effective (substantially equivalent) to a legally marketed device

- **HUD**
  - Approval based on evidence of safety and probable benefit
  - Requirement to establish “reasonable assurance of effectiveness” waived
IDE/HUD Important Differences

- Device is approved: not investigational
- “Use” of HUD is according to label
  - Use of IDE is in the context of research
- Physician/clinician using device is not a “PI”
  - Unless HUD is being used in a clinical investigation
- IC is at the discretion of the IRB
- Serious adverse events are reported as MDRs (21 CFR 803), not UADEs
IRB Review of HUDs

- **Initial Review**
  - Requires review and approval at convened board
  - May approve without restrictions, for groups that meet certain criteria, under a treatment protocol or on a case by case basis

- **Continuing Review**
  - Not to exceed one year
  - May require a summary report after specific number of patients before additional use
  - May be conducted by expedited review procedures
FDA Guidance

Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff

- Humanitarian Device Exemption (HDE) Regulation: Questions and Answers
- Document issued on July 8, 2010
- Draft guidance issued on March 18, 2014
30. “What adverse event reporting requirements apply to HUDs?”

- Device user facilities and manufacturers are required to submit medical device reports to FDA and to the “IRB of record.” Such adverse events are filed when the HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Serious injury means:
  - An injury or illness that if life-threatening
  - Results in permanent impairment of a body function or structure
  - Necessitates medical or surgical intervention to preclude the above

- These reporting requirements are already in place for medical devices under the Medical Device Reporting (MDR) Regulation at 21 CFR 803
MDR vs. UADE

MDR: Device may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Serious injury means:

- An injury or illness that if life-threatening
- Results in permanent impairment of a body function or structure
- Necessitates medical or surgical intervention to preclude the above

UADE: Any serious adverse effect on health or safety, any life-threatening problem or death

- Caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application
- Or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects
39. “How does an IRB distinguish between the use of a HUD and the study of a HUD in a clinical investigation (i.e., research)?”

- An HDE holder may collect safety and effectiveness data in a clinical investigation for the HDE-approved indication(s) without an IDE.

- Clinical investigation of a HUD for a different indication must be conducted under IDE regulations:
  - Requires IRB approval
  - If the device is significant risk (SR), an IDE is required
  - To date, most HUDs are SR devices
    - FDA’s list of approved HDEs can be found here: FDA’s HDE site
40. “What if the HDE holder decides to collect safety and effectiveness data in a study to support a PMA for the HDE-approved indications?”

- No IDE is required since its use is as labeled
- BUT must comply with all the IDE regulations at 21 CFR 812—in addition to the requirements for IRB approval (21 CFR 56) and protection of human subjects (21 CFR 50)
  - IRB approval of a HUD for labeled use is not the same as IRB approval for investigational use of a HUD (within its approved indication) to collect safety and effectiveness data
    - This means that IC for labeled use is at IRB’s discretion; IC for investigational use is mandated
  - Decision tree provided [here](#)
41. “Does an IRB have to make significant risk/non-significant risk determinations when reviewing HUDs?”

- Generally no, because:
  - An investigation using the HDE according to its approved indication is exempt from IDE regulations
  - To date, all HUDs when studied for uses other than labeled have been SR devices requiring an IDE
    - As such most sponsors have obtained an IDE before beginning such studies
  - HOWEVER: IRBs should be alert to an application for a study of a HUD for a new indication that does not come with an IDE
    - Only in this case does the IRB need to make the SR/NSR determination
44. “How should an IRB evaluate requests for approval...?”

• Follow 21 CFR 56 (IRBs) as much as possible, including:
  o Review risks as found in product labeling and assure risks are minimized and reasonable in relation to proposed use of the device
  o You should have policies and procedures in place for this review and approval, including whether your IRB requires a consent document for the use of the HUD
44 cont. “How should an IRB evaluate requests for approval...?”

To conduct such a review, the following documents should be included:

- Copy of HDE approval order
- Device description
- Product labeling
- Patient information packet and/or sample consent form
- Summary of proposed use
- Description of any screening procedures, HUD procedures and follow-up tests or procedures
45. “To what extent should an IRB exercise oversight of clinician responsibilities in the use of a HUD?”

- Since the FDA has determined safety and probable benefit, IRB is not required to review and approve each use.

- However, it may specify limitations on use, such as:
  - Base use on one or more measure of disease progression
  - Prior use and failure of any alternative treatment
  - Reporting requirements to IRB or IRB Chairperson
  - Appropriate follow-up precautions and evaluations or criteria

- Helpful to employ input from members with appropriate expertise.
47. “Why does the FDA suggest continuing review by expedited review?”

- It is a legally marketed device and no safety/effectiveness data is being systematically collected as would be in research.
- Chair or designate should “thoughtfully consider risk and benefit information” (usually contained in annual reports) and MDR reports.
- IRBs may develop their own policies on continuing review and perform this review at a convened meeting.
49. “What does an IRB have to know about Medical Device Reporting (MDR)?”

- That such reporting is required both by HUD regs (814.126a) and device regs (803)
- That such reports are submitted both to the FDA and the “IRB of record”
50. “What should an IRB consider with respect to the health care provider(s) who will use the HUD?”

- That they are qualified through training and expertise to use the device
- The original HDE order may mandate specific training, or the HDE holder may do so (usually in IFU)
  - All original HDE orders can be found on FDA’s HDE website
  - 64 listed, 59 currently active HUDs
HUD #060003

• “The labeling shall specify the training requirements for practitioners who may use the device as approved in this order”
HUD #060003

• CAUTION:
  o “This device should be used only by physicians with a thorough understanding of angiography and percutaneous neurointerventional procedures”
  o “This device should be used only by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiography techniques and super-selective embolization”

• TRAINING:
  o “Serious, including fatal consequences could result with the use of…. Contact your ... sales representative for information on training courses”
What About HSP Training?

- Often a bone of contention
  - Clinicians may not be researchers
  - Device is not investigational
  - In what way is human subjects protections training relevant?

- Possible solutions:
  - Full HSP training
  - HUD-specific training
    - CITI does have a supplemental HUD module
  - Documentation of device-specific training
FDA Guidance Highlights

Things the IRB is NOT required to do or review:

• 52. Monitor number of uses per year
• 53. Audit or review medical records of HUD recipients
• 54. Request justification of charges (This falls under FDA’s purview only)
• 55. Review charges for HUD
• 56. Function as a DMC
• 57. Concern itself with FWAs (unless it’s a clinical investigation)
58. “What information should be given to patients before they receive a HUD, and should patients consent to the HUD use?”

- “Neither the Act nor the regulations require informed consent from patients for the use of a HUD”
  - An IRB may chose to require IC that is consistent with the approved labeling
  - Most HDE holder develop patient information packets
    - If such is provided, the IRB must assure its use
  - Many institutions require a surgical or procedural consent
  - If the HUD is being studied in a clinical investigation, IC is required in accordance with 21 CFR 50
59. “If an IRB requires a written consent document..., what information should be included?”

- Much of the info from the HDE holder’s information packet if provided
- If not provided, include the following:
  - An explanation that the HUD is designed to diagnose or treat the disease or condition described in the labeling and that no comparable device is available
  - A description of any ancillary procedures
  - A description of the use of the HUD
  - All known risks and discomforts
  - An explanation of how the HUD works
  - A statement that as a HUD, effectiveness has not been demonstrated
  - Whatever else the IRB deems important
61. “What should IRBs tell a physician who wants to study a HUD for a new indication?”

- Get an IDE
HUDs and Research

- **Within labeled indication (e.g. collection of safety and effectiveness data):**
  - Constitutes research
  - HSP regs apply (21 CFR 50)
  - IRB review regs apply (21 CFR 56)

- **Outside approved indication (new indication):**
  - Constitutes research
  - HSP regs (21 CFR 50) apply
  - IRB review regs (21 CFR 56) apply
  - IDE regs apply (21 CFR 812)
A physician has used a HUD for its labeled use and sees a possible application for another indication. He would like to demonstrate its effectiveness for this use. Which of the following would NOT be included in his next steps:

- a) Communicate with the HDE holder
- b) Obtain an IDE
- c) Pilot the procedure
- d) Follow HSP/GCP regs
A physician has used a HUD for its labeled use and sees a possible application for another indication. He would like to demonstrate its effectiveness for this use. Which of the following would NOT be included in his next steps:

a) Communicate with the HDE holder
b) Obtain an IDE
c) Pilot the procedure
d) Follow HSP/GCP regs
Putting it Together

A HUD malfunctions during deployment and the patient suffers adverse effects. What next steps should the clinician take?

a) Fill out the IRB’s SAE form and report it to the IRB and HDE holder within 24 hours

b) Go to the FDA’s MedWatch site, download and complete an FDA form 3500A or eMDR report as instructed in 21 CFR 803
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Decision Tree: Research with HUDs
Is the HUD use necessary to prevent death or serious harm to a patient?

No

IRB review of application for use of HUD in the facility (see questions 41-47)

Is HUD to be used for HDE-approved indication(s) only?

No

Is HUD being used as part of a clinical investigation?

No

Follow procedures for emergency use of HUD (see questions 64, 65)

Yes

Will safety or effectiveness data be collected?

No

HUD use is not a clinical investigation (see question 39).

Yes

HUD use is a clinical investigation. 21 CFR Parts 50 (protection of human subjects) and 56 (IRB review) apply; no IDE is required for study of approved indication(s) (see questions 39-41).

IRB review process is up to the IRB; IRBs should be cognizant that FDA has made a determination of safety and probable benefit for use of HUD only within its approved indication(s) (see questions 45, 65).
Is the HUD use necessary to prevent death or serious harm to a patient?  

Yes: Is there sufficient time to obtain IRB approval prior to the HUD use?  
Yes: IRB review of application for use of HUD in the facility (see questions 41-47)

No: Follow procedures for emergency use of HUD (see questions 64, 65)

No: Will safety or effectiveness data be collected?  
No: HUD use is not a clinical investigation (see question 39).

Yes: Is HUD to be used for HDE-approved indication(s) only?  
No: Is HUD being used as part of a clinical investigation?  

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Is the HUD use necessary to prevent death or serious harm to a patient?  

Yes  
Is there sufficient time to obtain IRB approval prior to the HUD use?  

No  
Follow procedures for emergency use of HUD (see questions 64, 65)  

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No  
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Is the HUD use necessary to prevent death or serious harm to a patient?

Yes

Is there sufficient time to obtain IRB approval prior to the HUD use?

No

Follow procedures for emergency use of HUD (see questions 64, 65)

No

IRB review of application for use of HUD in the facility (see questions 41-47)

Yes

Will safety or effectiveness data be collected?

No

HUD use is not a clinical investigation (see question 39).

No

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Yes

Is HUD being used as part of a clinical investigation?

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Is the HUD use necessary to prevent death or serious harm to a patient?

Yes → Is there sufficient time to obtain IRB approval prior to the HUD use?

No → Follow procedures for emergency use of HUD (see questions 64, 65)

Yes → IRB review of application for use of HUD in the facility (see questions 41-47)

Is HUD to be used for HDE-approved indication(s) only?

Yes → Will safety or effectiveness data be collected?

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IRB review process is up to the IRB; IRBs should be cognizant that FDA has made a determination of safety and probable benefit for use of HUD only within its approved indication(s) (see questions 45, 65).
62. “What about HIPAA?”

- HIPAA allows use and disclosure for treatment purposes without an authorization
  - So use and disclosure of PHI for treatment (non-research) purposes does not require an authorization
- If used for research – authorization or waiver is required
FDA Guidance Highlights – Emergency Use

64. “When can a HUD be used without prior IRB approval?”

- If a physician in an emergency situation determines that IRB approval cannot be obtained in time to prevent serious harm or death, it may be used without prior IRB approval
  - Must report to IRB within 5 days and provide:
    - Written notification including identification of patient
    - Date of use
    - Reason for use

- Differs from emergent use after approval
  - This is subject to the IRB’s approval terms
HUD Emergency Use

Is the HUD use necessary to prevent death or serious harm to a patient?

Yes

Is there sufficient time to obtain IRB approval prior to the HUD use?

No

Follow procedures for emergency use of HUD (see questions 64, 65)

Yes

IRB review of application for use of HUD in the facility (see questions 41-47)

Is HUD to be used for HDE-approved indication(s) only?

No

Will safety or effectiveness data be collected?

Yes

HUD use is a clinical investigation. 21 CFR Parts 50 (protection of human subjects) and 56 (IRB review) apply; no IDE is required for study of approved indication(s) (see questions 39-41).

No

HUD use is not a clinical investigation (see question 39).

Is HUD being used as part of a clinical investigation?

No

Yes

IRB review process is up to the IRB; IRBs should be cognizant that FDA has made a determination of safety and probable benefit for use of HUD only within its approved indication(s) (see questions 45, 65).
65. “After IRB approval…can a physician use a HUD outside its approved indication(s) in an emergency or if s/he determines no alternative device exists?”

- Yes. However, since the FDA determined safety and probable benefit only for the approved use, the FDA recommends:
  - First check with the IRB before such use to review any institutional policy
  - The physician obtains informed consent and employs reasonable patient protections including:
    - Devising a schedule to monitor the patient that takes into consideration patient needs and lack of information regarding risks/benefits in this setting
  - Submit a follow up report to the HDE holder and IRB according to its policy

- Extent of IRB oversight in this situation is up to the IRB
- MDR reporting requirements apply
HUD Off-Label Use

Is the HUD use necessary to prevent death or serious harm to a patient?

- Yes: Is there sufficient time to obtain IRB approval prior to the HUD use?
  - Yes: Follow procedures for emergency use of HUD (see questions 64, 65)
  - No: IRB review of application for use of HUD in the facility (see questions 41-47)

- No: Is HUD to be used for HDE-approved indication(s) only?
  - Yes: Will safety or effectiveness data be collected?
    - Yes: HUD use is a clinical investigation. 21 CFR Parts 50 (protection of human subjects) and 56 (IRB review) apply; no IDE is required for study of approved indication(s) (see questions 39-41).
    - No: HUD use is not a clinical investigation (see question 39).
  - No: Is HUD being used as part of a clinical investigation?
    - Yes: HUD use is a clinical investigation. 21 CFR Parts 50 and 56 apply; IDE regulations at 21 CFR Part 812 apply (see questions 39-41).
    - No: IRB review process is up to the IRB; IRBs should be cognizant that FDA has made a determination of safety and probable benefit for use of HUD only within its approved indication(s) (see questions 45,65).
Getting It Right – IRBs

- HDEs vary in nature and use
  - Elective to emergent, low to high risk
- Status as non-investigational can confuse and result in mixed-messages
  - Forms and requests that don’t apply
  - Imposition of non-applicable requirements
- Regs and guidance allow IRB discretion in level of oversight
  - Can be employed to correspond with nature and use of specific HUDs
  - Overly rigid application can frustrate users and increase likelihood of non-compliance
Getting It Right

Don’t confuse HUD use with IND and IDE research

- IND/IDE Research
  - IND, IDE
  - Investigator
  - Protocol
  - SAEs, UPIRHSO
  - Informed Consent

- HDE/HUD
  - HDE order
  - Physician user/Clinician
  - IFU, Labeling
  - MDR
  - IC optional, patient booklet if provided
Getting It Right

- Institutional challenges
  - In some cases, devices and their use are managed, not by the research department, but by the surgical or cath-lab staff
    - May not understand IRB jargon or requests
    - Extreme reporting requirements guarantee non-compliance

- IRB challenges
  - Current forms contain many N/A questions and fields
  - May default to IDE regs, adding unnecessary burden to users
  - Regs don’t reference a “principal investigator” — all clinicians are responsible for their own use
An IRB has received an application to review a HUD. Which of the following questions are appropriate:

a) Who is the principal investigator?

b) How much will be charged for the device?

c) What specific training requirements are there for the use of the device?

d) What is the version date of the protocol?
An IRB has received an application to review a HUD. Which of the following questions are appropriate:

a) Who is the principal investigator?

b) How much will be charged for the device?

c) What specific training requirements are there for the use of the device?

d) What is the version date of the protocol?
During an intervention an emergent situation develops. A HUD is in stock. The physician has the requisite skills and experience but has not been approved to use it. What are her options?

a) Call around and see if she can find an approved user
b) Deploy the device
c) Report its use to the IRB within 5 days
d) Apply for future use
During an intervention an emergent situation develops. A HUD is in stock. The physician has the requisite skills and experience but has not been approved to use it. What are her options?

a) Call around and see if she can find an approved user

b) Deploy the device

c) Report its use to the IRB within 5 days

d) Apply for future use
A perforation occurs during a peripheral intervention. The physician believes the patient is in danger of serious harm or death. An approved HUD covered stent for cardiac vessel perforations is available. Which of the following is NOT required?
Putting It Together

a) Check with the IRB about any institutional policies if possible
   • If not: report to the IRB within 5 days

b) Obtain and document informed consent if possible
   • Employ and document any patient protection measures taken

c) Report to the HDE holder

d) Report to the FDA

e) Devise and follow a follow-up and monitoring plan
Putting It Together

a) Check with the IRB about any institutional policies if possible
   • If not: report to the IRB within 5 days

b) Obtain and document informed consent if possible
   • Employ and document any patient protection measures taken

c) Report to the HDE holder

d) Report to the FDA

e) Devise and follow a follow-up and monitoring plan
Conclusion

HUDs are not complicated

• When the differences from IDEs are understood and appreciated
• When processes for approval and use match the regulations and guidance
• When all parties involved want to get it right
Humanitarian Use Devices
It’s Not That Complicated
June 24, 2015

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