Ethical and Regulatory Considerations in Drug Development for IN Naloxone

Robert ‘Skip’ Nelson, MD PhD
Senior Pediatric Ethicist/Lead Medical Officer
Office of Pediatric Therapeutics, Office of the Commissioner
Food and Drug Administration, Silver Spring MD
<Robert.Nelson@fda.hhs.gov>

Indication for Naloxone

From the approved label:

- Naloxone hydrochloride (HCl) injection is indicated for the ***complete or partial reversal of narcotic depression***, including respiratory depression, induced by opioids.
- Naloxone HCl injection may be administered ***intravenously (IV), intramuscularly (IM), or subcutaneously***.
- Naloxone HCl is supplied as either a 0.4 mg/mL (single dose or 10 ml. multi-dose vial) and 1 mg/mL injection, for IV, IM and subcutaneous administration.

Intranasal (IN) administration of Naloxone hydrochloride is an unapproved use.†

† Note: This presentation is not about the "off label" use of Naloxone as part of clinical practice.

Context of Proposed Study Use

- Naloxone has been provided to individuals who are considered to be ***at risk for an acute opioid overdose***.
  - from prescription opioid pain relievers.
  - from accidental overdose of illicit opiates (e.g., heroin)
- Although ***IM administration*** is used, ***IN administration*** has some advantages with, for example, ease of administration, storage, and avoidance of needles. Alternatively, an IM auto-injector for Naloxone could be developed.
- The public health benefit of distributing IN or IM Naloxone to injection drug users (IDUs) appears to be largely from the recipient intervening in ***a witnessed overdose*** (i.e., using Naloxone on another person).

Who are the study subjects?

- "Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control." (21 CFR 312.3; cf. 21 CFR 50.3g)
- The person who receives IN Naloxone is a study subject. The person who administers IN Naloxone may or may not be a study subject (depending on the research question).
- Obtaining informed consent from the person given IN Naloxone to give administer to another person during a witnessed overdose does <u>not</u> meet the FDA requirement for informed consent from subjects prior to administration of an investigational drug.

What data may be necessary?

Bioequivalence: Does IN Naloxone administration achieve a ***comparable drug exposure*** to IM/IV administration of Naloxone? Would a study in healthy (i.e., non-opioid using) adults be sufficient?

•*A bioequivalence study* ***does not require the subject to be suffering from an acute opioid overdose****, and thus can be done using standard research procedures and informed consent.*

What data may be necessary?

Efficacy (and Safety): If we are unable to achieve comparable drug exposures using IN administration, must we perform a safety and efficacy study of the use of IN Naloxone?

•*An efficacy study of individuals* ***at risk from prescription opioid pain relievers*** *could be performed using standard research procedures and informed consent (even if IN Naloxone was given by others to the subject).*

What data may be necessary?

- An efficacy study of individuals at risk from ***accidental overdose of illicit opiates*** could be performed.
  - If IN Naloxone is administered only to the person receiving an "overdose kit" (with informed consent), the study may be performed using standard research procedures and informed consent.

However...

1. The main use of IN Naloxone appears to be for witnessed overdoses.
2. Excluding witnessed overdoses may be difficult, and reduce the study power given relative paucity of self-inflicted vs. witnessed overdoses.
3. Including witnessed overdoses means that the study subject has not consented to the administration of the investigational product. Such a study must be done under ***an exception from informed consent***.

What data may be necessary?

Actual Use Study: Even if IN Naloxone achieves a comparable drug exposure, would we need to do an "actual use" study to support wide distribution of an "overdose kit" to individuals ***at risk for an acute opioid overdose***?

•*Again, the inclusion of witnessed overdoses in such a study would require that the study be done under* ***an exception from informed consent****.*

Exception from Informed Consent

- Study protocol must contain a justification for:
  - Conducting the study in subjects who cannot provide informed consent (i.e., including witnessed events)
  - Selecting therapeutic window for administration of investigational product (i.e., within minutes of witnessed event)
- The human subjects must be in a life-threatening situation
  - Need not be immediately life-threatening or result in death; however, death likely unless course of disease is interrupted, and intervention required before consent is feasible
  - Must be emergent situation (e.g., not long-term or permanent coma)
- Collection of valid scientific evidence must be necessary to determine the safety and effectiveness of the intervention.

21 CFR 50.24 - see guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Exception from Informed Consent

- Available treatments are unproven or unsatisfactory
  - Unproven: lack of substantial evidence that treatment is effective
  - Unsatisfactory: drawbacks to the treatment (e.g., safety, partially effective, takes too long to work, limitations in targeted setting)
  - Arguably, use of IM Naloxone may be proven but is not satisfactory (absent development of an auto-injector).
- Obtaining informed consent is not feasible because:
  - Subjects not able to give informed consent due to medical condition;
  - Investigational product must be administered before consent from subjects' legally authorized representative feasible; and
  - No reasonable way to identify prospectively individuals likely to become eligible for participation in the clinical investigation.

21 CFR 50.24 - see guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Exception from Informed Consent

- Intervention must hold out the prospect of direct benefit to the subject receiving the intervention
  - Subjects are facing a ***life-threatening situation*** that necessitates intervention;
  - Information from appropriate animal and other preclinical studies support the potential for the intervention to provide a ***direct benefit to the individual subjects***; and
  - The ***risks associated with the investigation are reasonable*** in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

21 CFR 50.24 - see guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Exception from Informed Consent

- Additional protections of rights and welfare of subjects will be provided, including, at least:
  - Consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn (i.e., ***community consultation***);
  - ***Public disclosure*** to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
  - Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

21 CFR 50.24 - see guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Exception from Informed Consent

- ✓ An efficacy study of the use of IN Naloxone for complete or partial reversal of narcotic depression, including respiratory depression, meets all of the criteria for an exception from informed consent, provided that the research process includes community consultation and public disclosure.
- Note: EFIC unavailable for prisoners.

21 CFR 50.24 - see guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Community Consultation

- "There is no single acceptable way to accomplish or fulfill the community consultation requirements, nor will all studies require the same amount, type, or extent of community consultation activities."†
- Published literature contains data on views of appropriate community on use of IN Naloxone (i.e., generally favorable). It does not appear to be difficult to engage the affected communities in a discussion of a clinical trial of IN Naloxone for the treatment of an acute opioid overdose.

† 21 CFR 50.24 - see guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf

Examples of Community Consultation

- Appropriate "community" is protocol-specific
  - Key issue – building trust, mutual respect.
- Required feature: two way communication
  - Public meetings (town hall, existing community groups), community council, focus groups, face-to-face interviews
  - Random digit dialing telephone interviews, surveys (need opportunity for asking questions of research team)
- One way communications (i.e., press releases, brochures, newsletters, advertisements) are methods of "public disclosure."

Selected references on community consultation provided at the end of the presentation.

Public Access Defibrillation Trial

- Study Design (randomized buildings)
  - Control: training on-site, non-medical, lay volunteer responders to call 9-1-1 and perform basic cardiopulmonary resuscitation (CPR)
  - Intervention: training as above, addition of on-site deployment of automated external defibrillators (AEDs)
  - Primary outcome: survival of out-of-hospital cardiac arrest
- Subjects (two sets)
  - Volunteer layperson responders who received CPR or CPR/AED training; obtained prospective, written informed consent
  - Persons who suffer a suspected OOH-CA; requires EFIC
- Community consultation and public disclosure
  - Meetings, radio/TV/print media, telephone/electronic communication

Mosesso VN, Jr., LH Brown, et al. (2004). Resuscitation 61(1): 29-36.

Avoiding Community Consultation?

- Given that using IN Naloxone for witnessed events may have greater public health impact, and including such events may make clinical trial both more feasible and relevant, what is the ethical justification of excluding administration of IN Naloxone to non-consenting subjects simply to avoid the ethical requirement of consulting with the IDU community?
- From a public health perspective, one could argue that designing such a study to avoid the need for community consultation and public disclosure is unethical.

Do you need an IND?

- Clinical studies on the dosing, safety and/or efficacy of Naloxone <u>are</u> FDA-regulated (even if IND exempt).
- Commercial development of a novel formulation may benefit from conversations with FDA about the data necessary for an NDA submission (e.g., pre-IND meeting).
- An efficacy study of Naloxone requires an IND unless all exemption criteria under 21 CFR 312.2(b) are met.
  - Use of IDU population <u>not</u> exempt under 21 CFR 312.2(b)(iii).
  - A study performed under an exception from informed consent requires a separate IND under 21 CFR 312.20(c).

Challenge: Data Collection

- "FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety."
  - 21 CFR 312.22:
- A clinical trial of IN Naloxone must include ***measurable endpoints*** for efficacy, and ***adequate data collection*** for safety (i.e., adverse drug reactions, re-administration, morbidity and mortality), that are sufficient to allow for an assessment of safety and efficacy.

Selected EFIC References

1. Baren JM. and MH Biros (2007). "The research on community consultation: an annotated bibliography." Acad Emerg Med 14(4): 346-352.
2. Brasel KJ, E Bulger, et al. (2008). "Hypertonic resuscitation: design and implementation of a prehospital intervention trial." J Am Coll Surg 206(2): 220-232.
3. Longfield JN, MJ Morris, et al. (2008). "Community meetings for emergency research community consultation." Crit Care Med 36(3): 731-736.
4. Mosesso VN, Jr., LH Brown, et al. (2004). "Conducting research using the emergency exception from informed consent: the Public Access Defibrillation (PAD) Trial experience." Resuscitation 61(1): 29-36.
5. Nelson M, T A Schmidt, et al. (2008). "Community consultation methods in a study using exception to informed consent." Prehosp Emerg Care 12(4): 417-425.
6. Ramsey CA, B Quearry, et al. (2011). “Community consultation and public disclosure: preliminary results from a new model.” Acad Emerg Med 18(7): 733-740.
7. Raymond TT, TG Carroll, et al. (2010). "Effectiveness of the informed consent process for a pediatric resuscitation trial." Pediatrics 125(4): e866-875.
8. Richardson LD, I Wilets, et al. (2005). "Research without consent: community perspectives from the Community VOICES Study." Acad Emerg Med 12(11): 1082-1090.

Thank you.