OMIC
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A Risk Retention Group

Risk Management Recommendations

Sponsored by the American Academy of Ophthalmology

Research or the Practice of Medicine?

Anne M. Menke, R.N., Ph.D.
OMIC Patient Safety Manager

Purpose of risk management recommendations

OMIC regularly analyzes its claims experience to determine loss prevention measures that our insured ophthalmologists can take to reduce the likelihood of professional liability lawsuits. OMIC policyholders are not required to implement risk management recommendations. Rather, physicians should use their professional judgment in determining the applicability of a given recommendation to their particular patients and practice situation. These loss prevention documents may refer to clinical care guidelines such as the American Academy of Ophthalmology's *Preferred Practice Patterns*, peer-reviewed articles, or to federal or state laws and regulations. However, our risk management recommendations do not constitute the standard of care nor do they provide legal advice. Consult an attorney if legal advice is desired or needed. Information contained here is not intended to be a modification of the terms and conditions of the OMIC professional and limited office premises liability insurance policy. Please refer to the OMIC policy for these terms and conditions.

Revised 10/23/20

An ophthalmologist called OMIC's confidential Risk Management Hotline to inquire whether using Vitrase (hyaluronidase, Allergan/ISTA) for the treatment of vitreous hemorrhage (VH) was considered research. He informed us that it is FDA-approved as a spreading agent, and that using it for VH had been studied in clinical trials, which showed a benefit. However, the FDA did not approve clearance of VH as an indication. Similar questions arise when ophthalmologists start using approved drugs and devices for new indications, or when they develop a significantly different surgical technique. This discussion of how to distinguish between research and medicine should prove useful.

What is research?

Physicians who conduct research are subject to state and federal law, and so determining if one is engaged in research is an important determination to make. In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

produced the Belmont Report, which served as the foundation for federal laws.[1] It discussed the boundaries between practice and research and presented the basic ethical principles—respect for persons, beneficence, and justice—that apply to research on human subjects.

The Report notes that "the distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called 'experimental' when the terms 'experimental' and 'research' are not carefully defined."[1] The following table further clarifies the distinction between practice and research.

PRACTICE OF MEDICINE	**RESEARCH**
• Interventions designed solely to enhance the well-being of an individual patient or client • Intervention has a reasonable expectation of success • Purpose is to provide diagnosis, preventive treatment, or therapy to particular individual	• Activity designed to test an hypothesis, permit conclusions to be drawn, develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships) • Usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective

Status of innovative practice

The Belmont Report explained that an "experimental" procedure, that is, one that is new, untested, or different, is not automatically research. Nor, necessarily, is a significant departure from accepted or standard practice. The Report suggested, however, that radically new procedures should be made the object of formal research at an early stage in order to determine their safety and effectiveness. It is the responsibility of medical practice committees, it opined, to insist that major innovations be incorporated into a formal research project. Indeed, this self-policing is a hallmark of professionalism.

From a risk management and patient safety perspective, if you are not sure if what you are doing constitutes research, or if there is any element of research in the procedure or practice, you should consult with your local Institutional Review Board (IRB). If the activity is considered research, the IRB will help you determine what other steps you must take to protect the rights and safety of human subjects, as participants is research are called.

[1] The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research is available online at https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html; accessed 10/23/20.

Unapproved and "off-label" drugs and devices

The distinction between research and the "practice of medicine" can be particularly confusing when it comes to unapproved and "off-label" drugs and devices. The federal Food and Drug Administration (FDA) approves and regulates the production, sale, and clinical research of medical drugs and devices. It does not directly regulate the practice of medicine; this task is left to state medical boards.

Ophthalmologists are aware that once a device or medication is approved by the FDA, they may use it "off-label" for other purposes as part of the "practice of medicine" if 1) they are well-informed about the product, 2) base its use on firm scientific method and sound medical evidence, and 3) maintain records of its use and effects.[2] Physicians would be well-advised to use the checklist that follows to perform a risk analysis prior to using an unapproved or "off-label" drug or device to determine the patient safety and professional liability risks associated with its use.

RISK ANALYSIS CHECKLIST[3]

- What is the drug or device's FDA status?
    - Approved but not for intended use or route?
    - Unapproved but undergoing clinical trials under an IDE (Investigational Device Exemption) or IND (Investigation New Drug Exemption)?
    - Unapproved but not yet undergoing trials?
    - Unapproved and unlikely to undergo trials?
- Who is manufacturing the drug or device?
    - A manufacturer, outsourcing facility, or compounding pharmacy
        - Is the manufacturer, outsourcing facility, or compounding pharmacy reputable and known to you?
        - Does the manufacturer, outsourcing facility, or compounding pharmacy follow industry guidelines for sterility and quality assurance?
            - Keep material documenting the sterility and quality in your file on the drug or device
- Are you distributing or reselling it?
    - If the drug/device is labeled, promoted, or distributed in US, then it is regulated by the FDA and subject to pre-marketing and post-marketing regulatory controls to assure safety and effectiveness.
    - Distributing or selling greatly increases the risk of FDA action.

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[2] Food and Drug Administration. Guidance for Institutional Review Boards and Clinical Investigators: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices. 1998 Update, available online at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices; accessed 10/23/20.

[3] Adapted from Wittchow, Kimberly. When FDA Leaves Doctors to Their Own Devices. OMIC Digest. Volume 13, Number 2.Spring 2003, available at https://www.omic.com/when-fda-leaves-doctors-to-their-own-devices/, accessed 10/23/20.

- How are you using it?
    - Research:
        - Gathering new information on multiple patients for publication purposes, or to obtain approval for a new device or a new use of an approved device, is probably research and requires an IDE or IND.
            - See "Risk Management Recommendations: Retrospective Study of "Off-label Medications" below.
        - Part of an IDE or IND to collect safety and effectiveness data required to support the PMA (pre-market approval) application to the FDA
        - If considered research, follow federal and state requirements for:
            - Obtaining approval of an IRB for the trials or study
            - Obtaining informed consent of the human subject (this is usually waived for retrospective studies)
            - Disclosing any financial interests/incentives
    - "Practice of medicine"
        - Not for research AND
        - Not planning to gather new information for publication or approval purposes AND
        - Use based on firm scientific rationale and sound medical evidence
        - The "practice of medicine" is theoretically unregulated by FDA but some case law exists limiting the use of unapproved drugs/devices as part of the practice of medicine.
- What role does the drug or device play in the treatment?
    - Does the treatment consist primarily of using this drug or device?
        - If so, if approved for another use, and provides treatment results that are comparable to approved drugs or devices, considered "off-label" and legal if part of the "practice of medicine."
            - Example: Avastin for eye conditions
        - If so, but using it prior to any FDA approval, riskier
            - Example: Using Restylane for lip augmentation and facial contouring prior to approval was discouraged by OMIC.
    - Does the drug or device play an ancillary or supportive role in the performance of a procedure or treatment?
        - If so, there is less risk. In some cases, use might even be widespread and routine.
            - Example: Use of the dye, trypan blue, to stain the anterior capsule to facilitate visualization during cataract surgery when it was not possible to obtain it from an FDA-approved source
- What are the patient safety risks and how do you know about them?
    - Has a federal agency or state regulatory agency specifically banned the use of the drug or device because it was determined to be unsafe?
    - Is there sound medical evidence supporting the use of this drug or device?

    - Have peer reviewed articles been published supporting the use of this drug or device? If so, keep a file containing these articles and presentations.
    - Can its use be expected to bring good results without a higher complication rate?
    - If there is an increased risk, do a reasonable number of physicians in your specialty use the drug or device?
    - Is the use of the drug or device in the best interest of this particular patient?
- Is the procedure considered therapeutic or cosmetic?
    - Therapeutic use of an unapproved/off-label drug or device is less risky from a professional liability perspective than cosmetic use
    - If cosmetic or truly elective
        - Does the patient have reasonable expectations?
        - Has the patient had problems with other treating physicians in the past?
        - Is he or she set on a certain procedure because of advertisements and recent popularity?
        - What are the patient's motivations for having this procedure?
        - Does the patient fully understand what this procedure entails and the possible outcomes?
        - Does the patient understand that he or she will have to pay out-of-pocket not only for the procedure but also for any retreatment or follow-up?
- Verify coverage with your professional liability insurance carrier

Risk management recommendations: Use limited to the "practice of medicine

When drugs or devices are **first** used "off-label" for a new indication, there are often few if any adequate studies of the safety, efficacy, and long-term risks of their use. Exercise care in selecting patients, be familiar with the information that the manufacturer includes in the FDA-approved "label" detailing the indications, risks, and benefits that were determined during clinical trials, and monitor the patient for ongoing need, efficacy, and safety.

In order to comply with the FDA requirements pertaining to "off-label" use of a drug or device, keep a file of articles and other materials that support the decision to use the drug in question, and a record of the use and effectiveness.

In the informed consent discussion, advise the patient of the nature of the device, drug, or technique, the scientific basis for its use, and the expected risks, benefits, and alternatives. Consider recommending that the patient get a second opinion if the drug or device has significant risks, especially for truly elective procedures. If there are possible drawbacks or criticisms from other providers, share those. It is usually best to inform the patient of the FDA status, thus respecting the patient's right to obtain the information needed to make reasoned decisions about his or her own health care. If you believe that the approval status of the device will be a factor in the patient's decision, disclose the information.

Document the informed consent discussion of the risks, benefits, and alternatives, and include the fact that the patient was informed of the device's FDA status. If the treatment consists primarily of using the device, consider developing a specific consent **form** for the device that outlines the risks, benefits, and alternatives, and the FDA status, and give the patient a copy. OMIC has a sample consent form for off-label use available at https://www.omic.com/off-label-drugs-and-devices/.

Risk management recommendations: Retrospective studies of "off-label" use

When Avastin was first being used to treat macular degeneration, *Retina Times* published a discussion in a "Key Opinion Leaders" article. Many retina specialists were surprised to learn that the FDA considers the retrospective study of "off-label" use of a medication to be research.[4] Ophthalmologists engaged in studies of ophthalmic devices may want to rely upon their IRBs to determine when an IDE (investigational device exemption) is required. However, it is the FDA's position that any study of a drug would require an IND due to safety concerns, and that IRBs do not have the authority to waive the IND requirement.

Should physicians who have already completed retrospective studies of "off-label" medications without an IND fear malpractice lawsuits? While patients can sue their physician for any reason, they would have a very hard time winning such a case and proving harm. There are no patient safety risks in a retrospective research study. Furthermore, such studies do not violate privacy or confidentiality rights since the results are de-identified and the patient's identity is not disclosed. Indeed, IRBs routinely waive the consent requirements for this kind of research. The only risk would be FDA enforcement action, and that, too, seems unlikely.

Now that the FDA has clarified its position, ophthalmologists would be well-advised to analyze whether their "off-label" use constitutes research, and proceed accordingly. The two most important points to consider are your intent and the risk to the patient. The FDA Information Sheet entitled "Off-Label' and Investigational Use of Marketed Drugs, Biologics, and Medical Devices,"[2] differentiates between off-label use of approved (marketed) drugs as part of the practice of medicine and investigational use. When the intent is to practice medicine, that is, to treat an individual patient, no IND, IDE, or review by an IRB is required.

If the intent is to "develop information about the product's safety or efficacy," the use would be considered investigational. Moreover, in the case of a drug, an IND application would be required unless six conditions are met, of which I will discuss three. The first two address the intent of the investigational use. Studies whose purpose is to submit information to the FDA in support of a new indication for the drug or any other significant change in the labeling, or to support a significant change in the advertising of the product, would require an IND. The third condition that, if it were met, would allow a study of a drug to proceed without an IND requires that use "not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks)

[4] So You Want to Try Intravitreal Avastin. *Retina Times*, Fall 2005, pp. 18-21.

associated with the use of the drug product." According to information obtained from representatives of the FDA, this condition never applies to ophthalmic drugs, because of the potential toxic effect on the eye of active and inert ingredients. The take-away message for ophthalmologists who plan to publish the results of their clinical experience with "off-label" medications is to submit their proposed study to their IRB and apply for an INR.

Determining if you are engaged in research versus the practice of medicine involves careful analysis. The resources that follow may help. OMIC policyholders are encouraged to call our confidential Risk Management Hotline.

ADDITIONAL RESOURCES

- Department of Health and Human Services, Office of Human Research Protections (OHRP): http://www.hhs.gov/ohrp/, accessed 10/23/20.
    - Decision chart to determine if conducting research: http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm
- FDA Guidance for Institutional Review Boards and Clinical Investigators: https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors, accessed 10/23/20. Contains links to information about IRB rules, informed consent, drugs and biologics, medical devices, and federal research laws.
- FDA Good Clinical Practice and Clinical Trial Information: https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/selected-fda-gcpclinical-trial-guidance-documents, accessed 10/23/20.
- National Institutes of Health (NIH)
    - Bioethics Resources on the Web: Tutorials, Case Studies and Courses: https://www.niehs.nih.gov/research/resources/bioethics/resources/index.cfm, accessed 10/23/20.
    - Does your human subjects research study meet the NIH definition of a clinical trial? https://grants.nih.gov/ct-decision/index.htm

OMIC policyholders are invited to contact our confidential Risk Management Hotline for assistance. Please call 1.800.562.6642, option 4 or email us at riskmanagement@omic.com.