INVESTIGATIONAL DEVICE and/or DRUG USAGE IN RESEARCH & DEVELOPMENT SERVICE

1. **PURPOSE**: To establish a service level policy for the use of investigational devices and drugs, including the emergency or one-time treatment use of devices and/or drugs at the Portland VA Medical Center.

2. **POLICY**: The Food and Drug Administration (FDA) regulates clinical investigations (research) of products regulated by the FDA, including "foods, dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products." (21 CFR 56.101) VA investigators are expected to fulfill all of the responsibilities delineated in the Food & Drug Administration (FDA) regulations. Research regulated by the FDA may only be conducted at the PVAMC after:
   a. The Institutional Review Board (IRB) of record has received documentation that the research will be conducted under an applicable investigational new drug application (IND) or investigational device exemption (IDE); or formally determines and documents that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or formally determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.
   b. The research project and associated documentation have been approved by the IRB and the Research & Development Committee (R&DC), **excluding exceptions for the emergency or one-time treatment use of an unapproved medical device, investigational drug or drug for unapproved indication as outlined in this policy.**
   c. The patient or legally authorized representative has signed the VA Research Informed Consent Form (VA Form 10-1086), excluding exceptions from informed consent as outlined in this policy.

3. **DEFINITIONS:**
   a. A **Biologic** is a biological or related product, regulated by the FDA, including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Studies of unlicensed biologics are regulated according to the IND regulations, except in some cases when the biologic is in a combination product with a medical device.
   b. An **Investigation** is defined as a clinical investigation or research project/program involving one or more subjects to determine the safety or effectiveness of a device, intervention or drug [21 CFR 812.3(h)].
   c. An **Investigational Device** as defined by the FDA, is a device that is the object of an investigation [21 CFR 812.3(g)]. Investigational devices include transitional devices (21 CFR 812.3(r)) that are objects of investigations. According to VHA Handbook 1200.5, July 15, 2003, (3.j.), an investigational device may be an approved device that is being studied for an unapproved use or efficacy.
   d. An **Investigational Drug** is defined as a new drug or biological drug that is used in a clinical investigation, or an available drug used for non-approved indication. The term also includes a biological product that is used in vitro for diagnostic purposes.
   e. An **Investigator** as defined by the FDA is an individual who actually conducts a clinical investigation, i.e. under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. [21 CFR 812.3(i)].

f. A **Non-significant Risk Device** is one that does not present significant risk to the human subjects.
g. **Off-Label** means the use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label uses requires IND or IDE applications.
h. A **Significant Risk Device** is one that presents a potential for serious risk to the health, safety or welfare of the human subjects. [21 CFR 812.3(m)] Such a device is:
   (1) intended for use as an implant;
   (2) used in supporting or sustaining human life;
   (3) intended for a use that is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or
   (4) one that otherwise presents a potential for serious risk to the health, safety, or welfare of subjects.
i. **Sponsor** means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.
j. A **Sponsor-investigator** is an individual who both initiates and actually conducts, alone or with others, an investigation; that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.
k. An **Unapproved Device** is defined as a device that is used for a purpose or condition for which the device requires, but does not have, an approved application for pre-market approval under section 515 of the Federal Food, Drug, and Cosmetic (FD&C) Act [21 U.S.C. 360 (e)]. An unapproved device may be used in human subjects only if approved for clinical testing under an approved application for an Investigational Device Exemption (IDE) under section 520 (g) if the Act [21 U.S.C. 360(j)(g)] and 21 CFR 812. Medical devices that have not received marketing clearance under section 510(k) of the FD&C Act are also considered unapproved devices.

4. **RESPONSIBILITIES:**
   a. The **Associate Chief of Staff/Research & Development** is responsible for developing and managing policies and procedures related to the use of investigational devices and investigational drugs at the Portland VA Medical Center.
   b. The **Research and Development Committee** is responsible for assuring that all necessary subcommittee approvals are in place for studies involving investigational drugs and/or devices with human subjects and providing final approval of those studies.
   c. The **Institutional Review Board** is responsible for approving or disapproving research projects involving investigational drugs and/or devices in accordance with the procedures outlined in this policy.
   d. The **Chief of Staff** is responsible for evaluating and providing clearance, if appropriate, for the emergency use of a drug or device.
   e. **Principal Investigators** are responsible for:
      (1) Adhering to FDA regulations regarding investigational drugs and/or investigational devices, as well as the procedures outlined in this policy.
      (2) Submitting the scientific protocol and all required documentation, including the informed consent form and the IRQ Appendix E, or Investigational Drug Information Record (VA Form 10-9012) to the Research Service for IRB review and approval prior to beginning the study.
      (3) Submitting continuing review documentation and all adverse events to the IRB in a timely manner.

(4) Using the investigational device or drug only after notification of IRB and R&DC approval and informed consent is obtained from participants.
(5) Forwarding the original signed informed consent form (VA Form 10-1086) for each patient enrolled in the research project, emergency use protocol, or one-time treatment use protocol to the Research Service for scanning into the patient's electronic medical record. A copy of the informed consent form must also be provided to the research pharmacy. A copy must be given to the patient and the patient must initial the original signed consent form acknowledging receipt of a copy of the informed consent form.
(6) Providing secure storage for all investigational devices and/or drugs according to their storage requirements as outlined by the sponsor or, as appropriate, the research pharmacy.
(7) Providing accountability of all investigational devices and drugs and ensuring proper dispensing, utilization, storage, security and use of the investigational devices and/or drugs as defined in the research project proposal.
(8) Registering applicable studies on http://www.clinicaltrials.gov/; clinical trial information must be submitted for inclusion in the clinical trial registry databank. The applicable clinical trials are:
    a. Drug or biologic studies, with or without IND (except Phase 1, expanded access/compassionate use, or drug being used as part of routine care and not under study);
    b. Device studies, with or without IDE (except small feasibility studies, expanded access/compassionate use, or device being used as part of routine care and not under study).

5. **PROCEDURES:**
   a. **Research with Investigational Drugs:**
   (1) An investigational new drug application (IND) is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." An investigational drug must have an IND before it can be shipped, unless all of the following are true (i.e., clinical investigation of a drug is exempt from IND regulations if all of the following are true):
       a. The investigation is **not** intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
       b. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
       c. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
       d. The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50; and
       e. The investigation is conducted in compliance with the requirements of 21 CFR 312.7 and 8 (promotion and charging for investigational drugs).
   (2) A clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR 312 if the investigation does not otherwise require submission of an IND. Clinical investigations that are exempt from IND regulations still require IRB review and approval.
   (3) Even when there is no immediate intent to change product labeling or advertising, investigators who are planning rigorous, carefully controlled clinical investigations of off-

label uses of approved drugs or biologics should contact the FDA regarding obtaining an IND before submitting a protocol to the IRB.

(4) The PI must provide the PVAMC Research Pharmacy information on each subject receiving an investigational drug. With the informed consent form the Research Pharmacy will locate records in CPRS to assure that documentation is available on allergies, toxicities, and adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements. In cases where any of this information is missing, the Research Pharmacy will follow-up with the PI. The PI must also work with the Research Office to assure that the Research Pharmacy receives the following:
   a. Documentation of IRB and any other relevant approvals;
   b. A copy of VA form 10-9012, Investigational Drug Information Record, when applicable;
   c. A copy of the current approved protocol;
   d. Documentation of the IRB continuing review approval;
   e. Copies of sponsor-related correspondence specific to the drug(s) as appropriate;
   f. Copies of all correspondence addressed to the investigator from the FDA and other involved authorities) specific to the investigational drug(s) as appropriate;
   g. Notification to the Chief of Pharmacy Service, the Research Pharmacy and the IRB in writing when a study involving investigational drugs is suspended, terminated, or closed.

(5) The PI must comply with all dispensing requirements and all documentation requirements, including making relevant records accessible to the investigational drug pharmacist when requested.

(6) The PI must comply with all VHA pharmacy requirements regarding receiving, dispensing, storing and record-keeping for investigational drugs.

b. **Research with Investigational Devices:**

(1) An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization, or PMA) or cleared to market (via 510(k)) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk investigational devices must have an IDE issued by the FDA before they can be shipped. Non-significant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a non-significant risk device.

Research with investigational devices falls into three categories:
   a. Investigations of significant risk devices to determine safety and effectiveness.
   b. Investigations of non-significant risk devices to determine safety and effectiveness.
   c. Investigations exempted from the IDE regulations.

(2) The IRB must determine whether an investigational device is either Significant Risk (SR) or Non-Significant Risk (NSR).
   a. The determination of level of risk of the device is based on the proposed use of the device and not on the device alone.
   b. The designation of SR/NSR for a device is independent of the risk level designation of a study as a whole, and upon which the frequency of continuing review might be determined.
   c. The IRB makes its decision of significant or non-significant risk level of the device based on the review and evaluation of the following:
      i. the risk evaluation provided by the sponsor or sponsor-investigator investigator's brochure, if applicable federal regulations;

ii. the FDA Information Sheet, "Significant Risk and Non-Significant Risk Medical Device Studies,"
iii. any additional correspondence regarding the device that may be from the FDA, sponsor, and/or investigator;
iv. the nature of the harm that may result from use of the device;
v. if the subject must undergo a procedure as part of the investigational study, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device; and
vi. when applicable, the information and justification given by the sponsor for any NSR determination.

d. The rationale for the IRB's NSR/SR determination must be documented in the IRB minutes.

(3) Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to expedited procedures.

(4) Significant Risk Device Research

Applications for research on the use of a significant risk device must be accompanied by documentation from the FDA that includes a valid IDE number. This is captured on IRQ Appendix E. The IDE number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IDE numbers may not be validated with a device manual (which may serve multiple IDEs). If the sponsor or FDA has determined a device to be SR, the IRB must also consider the device to be SR during the IRB review. Research projects involving significant risk devices do not qualify for expedited review during the initial review.

Research projects involving significant risk devices may be considered for expedited review during the continuing review, if the IRB determines that the study meets one of the following three criteria:

a. The research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects;
b. No subjects have been enrolled and no additional risks have been identified;
c. The remaining research activities are limited to data analysis.

(5) Non-significant Risk Device Research

When research is conducted to determine the safety or effectiveness of a device, the PVAMC confirms, via IRQ Appendix E, that the device fulfills the requirements for an abbreviated IDE. Because NSR studies do not require an IDE, a clinical investigation involving an investigational device classified by the sponsor as NSR may be submitted to an IRB for review without an IDE. The sponsor should provide the IRB with a risk assessment and the rationale used in making its NSR risk determination. In cases that the investigator applies to the IRB for a non-significant risk determination for a device study, but the IRB determines that the device is significant risk, the IRB will notify the investigator, who must notify the sponsor (if applicable).

(6) Exempt Device Research
Clinical investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories:

a. A device legally marketed in the U.S. that is used for investigation in accordance with the indications in the FDA-approved labeling.
b. An in vitro diagnostic device if the testing is 1) noninvasive, 2) does not require an invasive sampling procedure that presents significant risk, 3) does not by design or intention introduce energy into a subject, and 4) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. An in vitro diagnostic device to support a premarket submission to the FDA is considered a human subject investigation regardless of whether samples to be used are individually identifiable or not. Such studies require IRB review, but may be eligible for expedited review and waiver of informed consent, when appropriate.
c. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more medical devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
d. A custom device (as defined in 21 CFR812.3 (b)), unless the device is being used to determine safety or effectiveness for commercial distribution.
e. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
f. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling the FDA reviewed under subpart E of part 807 in determining substantial equivalence.

c. **Sponsor-Investigator Research**
In reviewing research involving test articles, the IRB determines if a PVAMC investigator holds his or her own IND or IDE. If so, the IRB confirms that the investigator understands his or her additional responsibilities as the sponsor of the research, including reporting requirements to the FDA. The IRB may contact or site visit the sponsor-investigator as deemed necessary. A sponsor-investigator for an IND protocol must follow FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, and a sponsor-investigator for an IDE protocol must follow the regulations in 21 CFR 812. Sponsor-investigators of non-significant risk device studies have abbreviated sponsor responsibilities.

Sponsor-investigators who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE. In addition, they must document in writing that the product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.

d. **Expanded Access (also called "Compassionate Use") to Investigational Drugs and Devices**
(1) Investigational/Approved Drugs
Expanded access use (often referred to as "compassionate use") of drugs consists of the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy, when the primary purpose is to diagnose, monitor, or treat

a patient's disease or condition. The aim of expanded access is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

a. All expanded access use requires prior IRB review and approval. All expanded access programs use must meet the following basic criteria:
   i. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
   ii. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
   iii. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
   iv. In cases that the treatment is limited to a single patient, treatment is generally limited to a single course of therapy for a specified duration (unless FDA expressly authorizes multiple courses or chronic (i.e., ongoing) therapy. The treating physician should request an individual patient IND for treatment use on FDA form 1571 (specifying whether it is an emergency IND or individual patient IND). In these cases, the physician must also determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition, and the FDA must determine that the patient cannot obtain the drug under another IND or protocol.
b. Prior approval from the FDA is required for every category of the expanded access use program. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a "right of reference" to the IND (21 CFR 312.305(b)).
c. Reporting and monitoring requirements for investigators and sponsors exist for expanded access use drugs. These are outlined at 21 CFR 312.

(2) Investigational Devices

Compassionate use of investigational devices is typically approved for individual patients, but may be approved to treat a small group. Prior FDA approval is needed before compassionate use occurs.

a. The sponsor should submit an IDE supplement to the FDA requesting approval for a protocol deviation. The supplement should include the items outlined at 21 CFR 812.35(a)). The physician should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. The attending physician should devise an appropriate schedule for monitoring the patient(s), considering the investigational nature of the device and specific patient needs. The patient(s) should be monitored to detect any possible problems arising from the use of the device.
   i. A follow-up report should be submitted to the FDA as an IDE supplement in which summary information regarding patient outcome is presented.
   ii. Any problems which occurred as a result of the device use should be discussed in the supplement and reported to the IRB as soon as possible.
   iii. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

e. **Emergency Use of Unapproved Medical Devices or Investigational Drugs**

The FDA recognizes that emergencies may arise where an unapproved device or drug may offer the only possible life-saving alternative, but an IDE for the device or IND for the drug does not exist, or the proposed use is not approved under an existing IDE or IND, or the physician or institution is not approved under the IDE or IND. Using its enforcement discretion, FDA has not objected if a physician chooses to use such a device or drug in an emergency situation, provided that the physician later justifies to the FDA that an emergency actually existed. Decisions for "emergency" use may not be made in advance of the time the treatment may be needed based on the PI's expectation the IDE or IND approval procedures will require more time than is available.

Emergency use of a test article is exempt from prior IRB review and approval, provided that such emergency use is reported to the IRB in writing within five working days after the use. Expedited IRB approval is not permitted in emergency research. The FDA regulations allow for one emergency use of a test article at an institution. Any subsequent use of the investigational product is subject to prospective IRB review and approval.

The FDA regards emergency use of a test article, other than a medical device, as a "clinical investigation" and may require data from an emergency use to be reported in a marketing application. However, DHHS states "emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity." Thus, a patient receiving an emergency use of a test article is not considered a research participant by DHHS regulation. VA regulations in Handbook 1200.05, section 41, notes that emergency medical care is not research and does not need to be approved by an IRB and that emergency use of test articles must meet FDA regulations.

A principal investigator/physician must adhere to the following procedures regarding emergency use of unapproved medical devices, investigational drugs, or unapproved use of an approved drug:

(1) **Requirements for emergency use of a drug**

a. A patient is in a life-threatening or severely debilitating condition and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
b. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated.
c. Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
d. The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition.
e. The FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(2) **Requirements for emergency use of a device**

a. A patient is in a life-threatening or severely debilitating condition that needs immediate treatment.
b. There is no generally acceptable alternative available for treating the patient.
c. Sufficient time is not available to obtain prior FDA approval through existing procedures, prior to using the device because of the immediate need.

(3) **FDA Expectations of Physicians Regarding Decision of Use**
   a. Determine whether all requirements for emergency use have been met.
   b. Assess the potential benefits from the unapproved use of the device.
   c. Have substantial reason to believe that benefits will exist.
   d. Obtain an independent assessment by an uninvolved physician;
   e. Exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the IDE or IND procedures far enough in advance to avoid creating a situation in which such arrangements are impracticable.
   f. Obtain informed consent from the patient or the patient's legally authorized representative;
   g. Obtain institutional clearance from the PVAMC Chief of Staff or designee;
   h. Notify the IRB within five working days of the use of the drug or device; and
   i. Obtain authorization from the IDE or IND holder if an approved IDE or IND exists for the device or drug.

(4) **Notification to the Center for Devices and Radiological Health (CDRH)**
   a. The device developer must notify the Center for Devices and Radiological Health (CDRH) Program Operation Staff immediately after the shipment is made when a device is to be used in an emergency situation meeting all justifiable requirements.
   b. An unapproved device or drug may not be shipped in anticipation of an emergency.
   c. Business Hour Contact Information: 301.594.1190. Nights and weekends Contact Information: Division of Emergency and Epidemiological Operations: 202.857.8400

(5) **After Use Procedures**
   a. Report the use of the unapproved medical device or drug to the IRB within five days of usage and otherwise comply with provisions of the IRB regulations;
   b. Evaluate the need for the device or drug in the future, and if future use is likely, obtain IRB approval and an approved IDE or IND for future use; and
   c. If the device or drug does have an IDE or IND, notify the sponsor of the emergency use, or if an IDE or IND does not exist, notify the FDA of the emergency use and provide the FDA with a written summary of the conditions constituting the emergency, patient protection measures, and results.

f. **Waiver of Informed Consent on an Emergency Basis**

Even in an emergency situation, the investigator is required to obtain informed consent of the patient or the patient's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing the four items outlined below (21 CFR 50.23 (a)):

(1) The patient is confronted by a life-threatening situation necessitating the use of the test article.
(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the patient and there is a medical emergency or urgency.
(3) Time is not sufficient to obtain consent from the patient's legally authorized representative and there is a medical emergency or urgency.
(4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life and there is a medical emergency or urgency.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent determination required above in advance of using the test article, the determinations of the clinical investigator shall be made and, within five working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. All of the documentation

from the investigator and non-participating physician must be submitted to the IRB within five working days after the use of the test article.

6. **REFERENCES:** 21CFR50
   21CFR56
   21CFR312
   21CFR812
   Food and Drug Administration "Guidance for Institutional Review Boards and Clinical Investigators"
   Food and Drug Administration "Guidance on IDE Policies and Procedures"
   Stanford University HRPP Policy, Chapter 5: Investigational or Unlicensed Test Articles – Research with Drugs, Devices or Biologics

7. **CONCURRENCES:** Endorsed by the Research & Development Committee June 4, 2012.

8. **RESCISSION:** HRPP Policy & Procedure Investigational Device and/or Drug Usage, Endorsed by the R&D Committee 8/27/2007.

9. **FOLLOW-UP RESPONSIBILITY:** ACOS Research & Development Service (R&D).

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ACOS, Research & Development