

Corporation obtaining approval, the name of its representative, and the address of its main office

Name: Okayama University Hospital

Applicant: Hiroshi Makino

Address: Shikata-cho 2-5-1, Okayama City

#### Approved Type 1 Use Regulation

Name of the Type of Living Modified Organism	Nonproliferative and genetically modified human adenovirus type 5 that expresses Reduced Expression in Immortalized Cells; REIC (Adv/hREIC)
Content of the Type 1 Use of Living Modified Organism	Used in clinical facilities for human gene therapy, including storage, transportation, disposal and acts incidental to them
Method of the Type 1 Use of Living Modified Organism	<p>Address: Shikata-cho 2-5-1, Kitaku, Okayama City, Okayama Prefecture Name: Okayama University Hospital</p> <p>(1) The Adv/hREIC solution should be sealed in containers, transported to a clinical facility in the frozen state, and stored in a deep freezer in a P2 level laboratory at the facility (hereinafter referred to as “P2 laboratory”).</p> <p>(2) Thawing, dilution and dispensing of the frozen Adv/hREIC solution must be performed in a safety cabinet in a P2 laboratory. Storage of the diluted Adv/hREIC must be kept in a freezer in the P2 laboratory. Note that when the diluted Adv/hREIC or its frozen form is transported to another P2 level area through an open area, it must be kept in a container that is doubly sealed.</p> <p>(3) When disposing of the solution (including diluted solution) of Adv/hREIC, these must be disposed according to the infectious waste management protocol defined by Okayama University Hospital (hereinafter referred to as "the infectious waste management protocol") after the viral disinfection (by a cleaning with 0.18 or 0.24% of hypochlorous acid ; hereinafter referred to as “cleaning solution” or by an autoclave).</p> <p>(4) Adv/hREIC solution is diluted using buffer solution into designated volume for injection (hereinafter referred to as “Adv/hREIC injecting-solution”) in a safety cabinet in a P2 laboratory. Adv/hREIC injecting-solution must be double-sealed and transported to the IVR-CT room with a computed tomography system</p>

	<p>(hereinafter referred to as “CT room”). Adv/hREIC injecting-solution must be filled up into the devices with CT guided injection needles, syringes, and tubes (hereinafter referred to as “injection device set”) connected to the injection pump.</p> <p>(5) The administration of Adv/hREIC to a subject must be performed in the CT room through the already placed pleural catheter or by injecting the Adv/hREIC injection-solution under the CT guidance into the pleural cavity or the tumor in the patient with malignant mesothelioma. The needle should be withdrawn carefully so as to prevent the spillage or aerosol formation of Adv/hREIC injecting-solution. At the area surrounding the injection site, double layered dressings (disinfected and nonwoven) should be prepared.</p> <p>(6) Following the administration of Adv/hREIC, the wounds of the subject should be disinfected. The subject, who is wearing a mask and a dressing gown to prevent viral leakage, must be transferred from the CT room into a single room that is pressure-controlled not to be positive and has appropriate containment measures (hereinafter referred to as “single room”).</p> <p>(7) The injection device set including dressing clothes and gauzes used for the administration of Adv/hREIC at (5),(6) must be disposed after the viral disinfection in accordance with the infectious waste management protocol. The injection guide equipments such as a pump, ultrasound system, are re-used after viral disinfected. These processes should be done in the CT room. The injection device set must be transported within a double-sealed container when the disinfection processes could be needed in other open area. After injection, the floor of the CT room should be cleaned by the cleaning solutions. The treatment room is provided with ventilation system which can change the whole air of the room each 5 minutes (12 times in a hour) with HEPA filters.</p> <p>(8) The subject should be cared for in the single room until 24 hours after administration. In the case that Adv/hREIC was administered through the pleural catheter, the subject should be cared for in the single room until 24 hours after removal of the pleural catheter or until confirming the negative result of Adv/hREIC in the pleural fluid. When the subject enters the open area outside the single room for examinations, etc., procedures (blood samplings or excreta) should be minimum and the preventive measures including the</p>
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	<p>wearing of a mask and a gown must be compulsory to avoid viral leakage.</p> <p>(9) The excreta, etc. (including blood, body fluids, urine and feces) of the subject during the period of being taken care of in the single room should be appropriately disinfected and disposed of in accordance with the infectious waste management protocol. The excreta must be transported within a double-sealed container when the disinfection processes could be needed in other open area. Note that the excreta, etc., from the subject that are to be used as clinical samples should be handled in accordance with the handling of the Adv/hREIC solution as described above. The floor must be cleaned up by cleaning solutions when the excreta, etc. spill on.</p> <p>(10) During the period of being taken care of in the single room, invasive devices that have been used in the subject and those that have been in contact with excreta, etc., must be appropriately disinfected and then be disposed of in accordance with the infectious waste management protocol, or be washed sufficiently. The devices must be transported within a double-sealed container when the disinfection processes could be needed in other open area.</p> <p>(11) Before releasing the subject from being taken care of in the single room, confirm that Adv/hREIC is negative in the blood and the urine of the subject. If Adv/hREIC is detected, the subject should continually be cared for in the single room. Note that the floor of the single room after releasing the subject must be cleaned up by cleaning solutions whether the excreta spilled on or not.</p> <p>(12) If Adv/hREIC is detected in the blood or the urine of the subject, during the period of observation designated by the protocol of the gene therapy clinical study (title: the gene therapy clinical study for malignant mesothelioma using adenovirus vector expressing Reduced Expression in Immortalized Cells/Dickkopf-3 (REIC/Dkk-3) gene ) and at the time point after releasing the subject from being taken care of in the single room, the subject should be taken care of in the single room again immediately, and the same measures as in (8) to (11) above should be taken.</p>
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