OECD and ARRIVE 2.0 Guidelines for Testing Medical Device in Rat Models

1. Pre-experimental Planning

The pre-experimental planning phase must begin with a comprehensive ethical review process. All testing protocols must be submitted to the institutional animal care and use committee (IACUC) or equivalent ethical review body, including clear justification for animal use and demonstration that alternatives are not feasible. Ethical approval must be documented with a reference number for future reporting, and all procedures must align with the 3Rs principle of Replacement, Reduction, and Refinement. The study design must define primary and secondary outcomes clearly while conducting appropriate sample size calculations based on power analysis that specifies effect size, power (typically 80% or 90%), and significance level (typically 0.05). Researchers should consider variability from previous studies when available and thoroughly document the methodology and tools used for calculation. Proper randomization procedures must be implemented using appropriate methods (simple, block, or stratified) and documented in detail, preferably utilizing computer-generated randomization when possible. Appropriate control groups must be included, such as negative control (sham operation), positive control (if applicable), and vehicle control (if applicable). Blinding procedures should be implemented wherever possible, blinding experimenters to group allocation during procedures and outcome assessors to treatment groups, with clear documentation when blinding is not possible and justification provided. Test item preparation requires detailed documentation of medical device specifications including physical dimensions, materials/composition, manufacturing details, and sterilization method, along with preparation of positive control items according to validated procedures and documentation of the chain of custody for all test items.

2. Animal Selection and Housing

Animal procurement must source animals from reputable vendors with established health monitoring programs, documenting vendor name, location, and health status reports. Animals should have relevant health certificates, and transportation conditions and acclimation procedures must be fully documented. Strain selection should choose the rat strain most appropriate for the specific device testing with scientific justification documented and consideration of genetic background relevant to study endpoints. Complete genetic information including substrain must be reported. Sex considerations require inclusion of both male and female animals unless scientifically justified otherwise, with documentation of rationale if single sex is used and consideration of potential sex differences in the analysis plan. All sex-based differences in results must be reported. Age and weight considerations require use of animals of appropriate age for specific endpoints, documenting age at study initiation (both range and mean ± SD), reporting weight at study initiation (both range and mean ± SD), and considering age-related biological variables in study design. Housing conditions must maintain temperature at 20-26°C (with daily fluctuations documented), relative humidity at 30-70% (with daily fluctuations documented), and implement 12-hour light/dark cycle (with exact timing documented). Animals should be housed in appropriate caging with documentation of material and dimensions, number of animals per cage, bedding type and change frequency, environmental

enrichment items, and access to food and water, with all housing parameters documented in the final report.

3. Pre-surgical Procedures

Pre-surgical procedures must include an acclimation period of minimum 5-7 days before procedures, with health parameters monitored during this time and handling and habituation protocols documented. Baseline measurements including weight and clinical observations must be recorded. Pre-surgical fasting protocols should be implemented if required (typically 8-12 hours), maintaining access to water during fasting period, documenting fasting duration precisely, and recording pre-surgical weights. A complete pre-surgical health assessment must be performed, documenting criteria for exclusion based on health status, recording baseline physiological parameters, and ensuring animals meet all inclusion criteria before proceeding with surgical interventions.

4. Anesthesia and Analgesia Protocols

Anesthesia and analgesia protocols require careful selection of anesthetics appropriate for the procedure and duration, whether injectable (e.g., ketamine/xylazine, pentobarbitone) or inhalation (e.g., isoflurane), with scientific justification for anesthetic choice documented and doses, routes of administration, and timing specified. Anesthesia monitoring must assess depth of anesthesia using established parameters including pedal reflex, respiratory rate and character, heart rate, and oxygen saturation (if equipment available), with monitoring frequency documented (minimum every 5-10 minutes), proper body temperature maintained during anesthesia, and detailed anesthesia records kept for each animal. Analgesia protocols should implement pre-emptive analgesia when possible and select appropriate analgesic agents based on expected pain level, including opioids (e.g., buprenorphine), NSAIDs (e.g., meloxicam, carprofen), or local anesthetics (e.g., bupivacaine), with doses, routes, and administration schedule documented, criteria for rescue analgesia established, and detailed records of all analgesic administration maintained.

5. Surgical Procedures

Surgical procedures begin with surgical preparation using aseptic technique, sterilization of all instruments, preparation of the implantation site with appropriate antiseptic, and documentation of all preparation procedures. The device implantation procedure must follow a standardized surgical protocol documented in detailed step-by-step format, with precise anatomical location of implantation recorded, any deviations from standard protocol documented, duration of procedure recorded for each animal, and detailed surgical records maintained. Intraoperative monitoring requires continuous monitoring of vital signs during the procedure, documentation of any complications or adverse events, recording of fluid administration (type, volume, route), and maintenance of body temperature within physiological range. Recovery procedures must place animals in clean, warm recovery areas with continuous monitoring until ambulatory, recovery timeline documented for each animal, post-surgical care protocol implemented immediately, and time to full recovery recorded for each animal.

6. Post-surgical Monitoring and Care

Post-surgical monitoring and care in the immediate post-surgical period (0-24 hours) requires monitoring animals at minimum intervals of 2-4 hours, assessing pain using validated scoring systems that evaluate postural changes, behavioral changes, and physiological parameters, documenting administration of fluids and medications, implementing special feeding/hydration if needed, and maintaining appropriate environmental temperature. Ongoing monitoring (>24 hours) must assess animals daily at minimum, document body weight changes, monitor the wound/implantation site for inflammation, infection, dehiscence, and device migration, document food and water consumption, assess behavior and activity levels, and record any signs of distress or pain. Humane endpoints must be clearly defined with specific criteria for early euthanasia including weight loss >20% of pre-surgical weight, inability to eat or drink, signs of severe pain unrelieved by analgesia, and specific complications related to the procedure, with the decision-making process for implementing endpoints documented, any unscheduled euthanasia recorded with detailed justification, and all early terminations reported in the final analysis.

7. Endpoint Assessments

Endpoint assessments must include regular clinical assessments with physical examinations, systematic documentation of all clinical observations, assessment of device function according to protocol, and recording of body weight and general condition at defined intervals. Laboratory assessments should collect blood samples at predetermined timepoints for analysis of hematology parameters (complete blood count, differential white cell count) and clinical chemistry parameters (liver function tests, kidney function tests, electrolytes, and other relevant parameters), with sample collection procedures documented in detail and sample processing and analytical methods recorded. Pathology assessments require complete necropsy at study termination, documentation of organ weights (absolute and relative to body weight), collection of tissues according to standardized protocol, processing of tissues using validated histological methods, and detailed assessment of device-tissue interface, with local tissue response evaluated using standardized scoring systems for inflammation, fibrosis, necrosis, and foreign body reaction, potential systemic effects evaluated, and all procedures and findings documented in detail. Functional assessments should perform validated behavioral tests appropriate for endpoints, assess specific physiological functions relevant to the device, document testing protocols in detail, record environmental conditions during testing, and blind assessors to treatment groups when possible.

8. Data Collection and Management

Data collection and management procedures require the use of standardized forms or electronic systems for all data collection that include animal ID, date, time, and observer for all records, documenting both raw data and derived values, maintaining source documentation for all measurements, and implementing quality control procedures for data entry. Sample management must label all samples with unique identifiers, document sample collection, processing, and storage conditions, maintain chain of custody for all samples, and record any deviations from sample handling procedures. Data management protocols should implement data validation procedures,

document data entry verification processes, establish secure data storage systems, create regular data backups, and maintain an audit trail for any data modifications to ensure data integrity throughout the study.

9. Study Termination and Reporting

Study termination and reporting procedures must use euthanasia methods consistent with AVMA guidelines, documenting the method in detail (agent, dose, route), confirming death using appropriate secondary methods, and recording time and date of euthanasia for each animal. Statistical analysis must analyze data according to pre-specified statistical plans, document handling of missing data, address any protocol deviations in analysis, report both absolute and relative effects with precision estimates, present variability using standard deviation or confidence intervals, and include both raw data and derived values when appropriate. Reporting requirements following ARRIVE 2.0 guidelines must report study design details including sample size calculation, randomization procedure, and blinding methodology; animal characteristics including species, strain, sex, age, weight, source, health status, and housing and husbandry conditions; experimental procedures detailing what was done, how it was done, when it was done, where it was done, and why it was done; and results showing numbers analyzed in each group, reasons for any exclusions, and outcomes and estimation with precision (e.g., confidence intervals), along with adverse events, protocol modifications, discussion of limitations and implications of findings, and statements on ethical approval and guidelines followed.

10. Quality Assurance

Quality assurance measures must include protocol compliance with regular monitoring of protocol adherence, documentation of any deviations with justification, implementation of corrective actions as needed, and maintenance of documentation for all monitoring activities. Personnel training requirements must document qualifications and training of all staff, verify surgical competency before study initiation, implement standardized training for specialized procedures, and maintain training records for all personnel. Equipment calibration and maintenance procedures must calibrate all measurement equipment according to schedule, maintain service records for all equipment, document calibration procedures and results, and verify equipment function before critical measurements. Study documentation must maintain a complete study file including protocol and amendments, IACUC approval, standard operating procedures, raw data, analyses, correspondence, and final report, ensuring documentation meets GLP standards if applicable, and implementing secure archiving procedures for long-term data preservation and access.