# Dogs and NAMS in Cardiovascular Safety Testing

When a new drug is developed, scientists must test whether it could cause dangerous changes to the heart's electrical activity before it is ever given to a human. Under international guidelines (ICH S7A and S7B), this requires testing in a non-rodent animal, most commonly beagle dogs or c ynomolgus monkeys, that have had a small wireless telemetry device surgically implanted to continuously monitor their heart rhythm, blood pressure, and heart rate. The animal is given the drug and scientists watch for changes to the QT interval—a key measure on an electrocardiogram (ECG) that reflects how long it takes the heart to electrically "reset" between beats—because prolonging it is a well-established warning sign for dangerous arrhythmias.

Alongside animal studies, researchers use a cell-based lab test called the hERG assay that checks whether the drug blocks a specific heart channel that can often cause QT prolongation *(see NAMs examples below)*. Together, these two tests—a "negative" hERG result and a "negative" animal QT result—form the current regulatory gold standard known as the "double negative," which gives regulators confidence that a drug is unlikely to cause serious heart rhythm problems in people.

Dogs and monkeys are used because their heart electrical systems are similar enough to humans' to be informative, and the implanted telemetry allows recordings in a freely moving, unstressed animal, which is considered far more physiologically relevant than restrained or anesthetized animals. This testing is required globally before any new drug can be given to human volunteers in a clinical trial.

Examples of NAMs Used ***Alongside*** Animal Studies:

- **hERG Assay:** The human Ether-a-go-go Related Gene (hERG) assay is a non-animal technique that evaluates the movement of potassium of the hERG channel protein in the heart. This test is essential in drug development to determine if a new compound/drug blocks this important channel, which can cause dangerous cardiac arrhythmias.
- **CiPA:** A framework called the Comprehensive in vitro Proarrhythmia Assay (CiPA) uses human stem cell-derived heart cells (hiPSC-CMs) and computer models of the human heart's electrical activity to predict arrhythmia risk. Regulators now formally recognize these methods as meaningful contributors to the overall safety picture, particularly for reducing the need for large dedicated human clinical QT studies.

However, the hiPSC-CM technology still has maturation limitations. For example, lab-grown cells don't fully replicate the electrical behavior of adult human heart cells, and in silico models—while validated for a defined set of reference compounds—have not yet been accepted as a standalone substitute for animal studies across all drug types and contexts.

Regulatory References:

- ICH S7A: Safety Pharmacology Studies for Human Pharmaceuticals (2001)
- ICH S7B: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (2005)
- ICH E14/S7b Q&A (2022): Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential – Questions and Answers

Literature:

- Vargas et al., (2015): Evaluation of drug-induced QT interval prolongation in animal and human studies: a literature review of concordance
- Garrido et al., (2020): hERG toxicity assessment: Useful guidelines for drug design
- Valentin et al., (2022): The Challenges of Predicting Drug-Induced QTc Prolongation in Humans
- Matos et al., (2026): Predictive value of the hERG assay for anticipating the arrhythmogenic potential of new drugs