The primary cause of drug removal from development has oscillated between hepatotoxicity and cardiotoxicity, however cardiotoxicity has consistently moved to the top of the list over the last two decades. Cardiovascular adverse events, referenced in a summary by Valentin and Redfern (SOT 2017), describes the following: post marketing (49%), registration (38%), Phase II (28%) and Bioequivivalence (27%). As such there has been a need to develop new paradigms to reduce this trend. Is the current paradigm effective for assessing cardiovascular safety? What changes are needed to improve the current paradigm for assessing cardiovascular safety? This poster describes an integrated cardiovascular de-risking paradigm with a focus on the biomarker and functional endpoints that translate to the clinic. It looks at the potential of a drug to develop an arrhythmia compared to the current ICH S7B guidance for assessing compounds based on the potential to block hERG and to prolong the QT (QTc) interval of the ECG of a non-rodent species, along with assessing heart rate and blood pressure.

## Proposed Paradigm – Integrated Approach

### Biomarkers

**Biomarkers** (blood, protein and perfusate) are critical data points to include with cardiac functional and structural measurements. Myocardial dysfunction through hemodynamic stress, resulting from autonomic activation in heart rate and/or blood flow, results in the release of enzymes in an attempt to restore normal circulatory homeostasis. Hemodynamic stress is a biological response to damaged cells that produces a protective response leading to and stimulating cardiac remodelling and fibrosis. Myocardial cell damage may result progressively from cell membrane leakage to necrosis, which may result in early detection of cytosolic cardiac troponins.

**MYOCARDIAL DYSFUNCTION – HEMODYNAMIC STRESS**
- Stretch response and “hard work”, volume overload (heart failure)
- Pro-bradykinin peptides
- NT-proBNP (degraded form)
- Associated with left ventricular dysfunction
- Total renin peptide
- Modulation (non-specific), combination assessment with TCA
- Inflammation and vasodilation (multifactorial)
- Stretch response and pressure overload – Pressure dysfunction
- Lactic acidosis
- Secreted by macrophages, reactive to inflammation, fibrosis and remodeling
- Correlates with left ventricular diastolic dysfunction

**CORONARY VASCULAR INFILTRATION**
- hCYP – exclusive of future myocardial infarction, part of risk assessment
- Acute phase reactants
- Increases with inflammation (MI and taurine)
- IL-1β – proinflammatory
- TNF-α – proinflammatory, effects on inotropy
- L-1 – proinflammatory
- MABP – collateral pressure within the vascular wall
- Diastolic dysfunction

**MYOCARDIAL CELL DAMAGE AND ISCHEMIA**
- hCt
- hCtT
- Time course
- sST2
- α-smooth muscle
- TnI
- TnT
- TRPC (transient receptor potential)
- Systolic (contraction) and Diastolic (relaxation) dysfunction:
  - heart rate
  - diastolic blood pressure
  - oxygen supply/demand
- Calcium (levels)
- Echocardiography

**Biomarkers** (blood, protein and perfusate) are critical data points to include with cardiac functional and structural measurements. Myocardial dysfunction through hemodynamic stress, resulting from autonomic activation in heart rate and/or blood flow, results in the release of enzymes in an attempt to restore normal circulatory homeostasis. Coronary vascular inflammation is a biological response to damaged cells that produces a protective response leading to and stimulating cardiac remodeling and fibrosis. Myocardial cell damage may result progressively from cell membrane leakage to necrosis, which may result in early detection of cytosolic cardiac troponins to cardiac troponin complexes being detected in the blood or perfusate.

**6 Cardiovascular Assessment - Toxicology**

This process can further supply information for the repeat dose toxicology studies with regard to cardiovascular endpoints and biomarkers. Applying these concepts while investigating the cardiovascular system in repeat dose toxicology studies may provide the data to support optimizing implantable telemetry with left ventricular pressure capability via snap and ECG collection, as well as, provide the timing of when to sample the blood or tissues for the presence or absence of biomarkers, Lastly, utilizing imaging modalities as clinical translational tools can provide real-time progression of effects related to cardiac structural changes.