**Table S1. Key Design Elements Common to TQT Studies and Early Phase QT Assessment**

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| Standardized Subject handling | * Rest ≥10 min before ECG recording * The conditions of ECG recordings should be strictly matched for all dose cohorts * Record ECG prior to blood draws, vital signs, or PD assessments * Meals exert significant effects on the QTc. The timing and content of meals should be standardized across all arms and study visits used for QT assessment. |
| Robust ECG acquisition and measurement | * Preferable to collect digital ECGs using the same model of calibrated ECG machine for each subject. * Replicate (>3)recordings at each time point * Readers of ECGs should be blinded to time and treatment and all ECG’s in a single patient should be analyzed by the same reader. All ECGs from one subject should be measured using the same lead when a single lead analysis is performed * Alternatively, validated fully automated ECG analysis may be preferred to manual overread to avoid bias and remove the need for a positive control. |
| Timing of ECGs | ECG sampling timepoints should be sufficient to characterize the QTc effect of a drug throughout the dosing interval. Special care should be taken to perform ECG recordings at time points around the Cmax (for both parent drug and major metabolites). The 24-hour postdose ECG timepoint should also be implemented for a single dose trial to assess the impact, if any, on hERG channel trafficking or the effect of metabolites.  Although the E14 guidance discusses time-matched pharmacokinetic-ECG collection, exact time-matching in practice is impossible. For this reason, pharmacokinetic samples should be collected immediately after the time of ECG extraction in order to avoid autonomic changes in heart rate associated with blood sampling. The validity of the time window between the PK and ECG samples will depend on the rate of change of the PK profile. For drugs with slower rates (e.g., monoclonal antibodies), longer time windows may be acceptable.  ECGs collected at steady state are needed for drugs or clinically meaningful metabolites that accumulate after repeated dosing |