**BACKGROUND**

Screening for drug-induced cardio toxicity is a vital aspect of drug development, especially the effect a drug has on QT interval (QT). Accurate recording, measurement, and calculation of QT is necessary for cardiotoxicity analysis, yet many aspects of these processes are subjective, and techniques vary greatly between researchers and studies. Some experts of QT measurement that may be affected by differing methods include: identifying the end of the T wave, correcting QT based on heart rate (QTC), as well as the collection and summation of ECG time points. While the effects of different T wave characterization and QT calculation methods have been previously explored in the literature, it is still necessary to evaluate the effects of different analysis methods and identify potential industry standards that can minimize the number of data points needed without compromising model prediction.

The collection of telemetry ECG data yields hundreds of datapoints per minute as waveforms that each have multiple interval measurements. This means that in a 24-hour study, there will be more than 100,000 datapoints per animal per treatment. To manage this overwhelming amount of information, many techniques have been used to summarize ECG data. Most commonly, the data is minimum summarized into 1-minute averages, which are then treated as the smallest sub-units. These 1-min averages are then further summarized by techniques that will vary by researcher. One example of these summary techniques is the practice of averaging each 1-min datapoint in groups of predetermined time intervals. Another summary technique that is commonly used is the selection of a 3-minute datapoint that is closest to predetermined time points. These methods can vary in any or all of the following characteristics: number of total observations, the number of groups, and the number of observations per group. Adjusting these characteristics can affect the variability and estimation of drug effect.

To demonstrate the differences between summarization methods, we used previously collected telemetry ECG data from an unrelated safety study on the effects of verapamil, quinidine, and quinidine in Canine (Beagle), Sache (Beagle mixes), and Non-Human Primates (Chimpanzee monkeys). There were 4 subjects per species, and each subject was treated according to the following dose schedule, with one week between treatments:

- **Animal ID:** 2001
  - Treatment: Vehicle
  - Dose 1: 0 mg/Kg
  - Dose 2: 10 mg/Kg
  - Dose 3: 30 mg/Kg
  - Dose 4: 100 mg/Kg

**METHODS**

For the purpose of this poster, we have chosen to focus on the Non-human Primate data for quinidine. The telemetry data included the QT intervals and RR intervals summarized as 3-minute averages, which were labeled as their time from dosing. The QT-intervals were then corrected for changes in heart rate using the following methods:

1. **Baart method:** \( QT_{E} = QT + RHR \)
2. **Fridericia method:** \( QT_{F} = \frac{QT}{\sqrt{RR} - 1} \)
3. **Van de Water method:** \( QT_{W} = \frac{QT}{RHR - 0.0077} \)

The different QCs from vehicle treatments were then graphed against RR and compared in order to identify the best correction method.

A pre-dose average (baseline) of the selected QT method (QTE) was then determined for each subject on every treatment by averaging the 1-minute datapoints between 90-minutes before dose to 10-minutes before dose. The baseline was then used to determine the percent of QTE change from baseline for every 1-minute datapoint.

These were then summarized as the default linear averages, or as aggregated 12-min, 30-min, 60-min and 120-min averages. The 1-min datapoints were also summarized by randomly selecting timepoints every hour, as well as at set time intervals ([0, 0.5, 1, 2, 4, 8, 12, 20] hours). Each random selection was performed three times to demonstrate the inherent variability of these methods.

All of these summarization techniques were then graphed, and Restricted Maximum Likelihood (REML) estimation was performed on each using the linear function from the trend package in the R/Bio) formula used was:

\[
\text{InePercentChange}_{\text{ECG}Dose} \sim \text{Time} + \text{Baseline} + \text{Subject}, \text{ID} + \text{Time:Subject}, \text{ID} + \text{data}
\]

**RESULTS**

**CONCLUSIONS**

1. While the quality of raw data will have the greatest affect on results, the choice of summarization methods can introduce error that may affect the results of a QT study.

2. To promote reproducibility, there is need for the introduction of standardized methods of summary and analysis for QT studies.

**FUTURE DIRECTIONS**

1. Further quantify the effects of different summary methods to identify which can most accurately characterize cardiovascular changes.
2. Explore the effects of diurnal rhythm and researcher interaction on results.
3. Determine the effects of summarizing ECG waveform data by number of waves instead of by minute of time.
4. Design in silico models to characterize control ECG data for different species in order to improve the accuracy of QT studies.

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**REFERENCES**