VivaQuant provides services to efficiently extract accurate, consistent, and predictive information from your ECG recordings. VivaQuant ECG analysis services use the patented VivaQuant MDSP algorithm that has been shown to accurately extract arrhythmia and interval information from noisy ECG recordings. Services include quantification of arrhythmia incidence and burden and measurement of PR, QRS, RR, QT, and QTc intervals. In addition, VivaQuant has partnered with Fossa Consulting, LLC to provide two types of ECG beat-to-beat analyses: QT beat-to-beat (QTbtb) for assessment of QT interval changes without use of correction factors or binning and ECG restitution for assessment of cardiac stress and proarrhythmia liability.

**Features**
- Report arrhythmias and ECG intervals to the highest standard of accuracy.
- Complete beat-to-beat analysis with supporting “cloud” plots.
- Restitution analysis with supporting “cloud” plots.
- Comparisons to traditional QTc measures.
- Fast and easy automated report generation.
- Evaluation by pharmaceutical scientists, physiologists, and statisticians with more than 75 years’ experience with ECG analysis, preclinical research, and drug development.
- Automatically computes confidence in an identified feature on a sample-by-sample basis.
- All results manually screened to the highest quality standards.
- Can engage client’s QA unit on studies requiring GLP compliance.

**Benefits**
- Reduces costs, speeds turn-around time.
- Superior decision support information.
- Low interval measurement variability provides excellent statistical power and flexibility.
- Renders beat-to-beat analyses practical and cost effective.
- Enables evaluation of data during periods of varying autonomic state that prohibit use of QTc.
- Preserves more information and provides more flexibility in data handling strategies by often eliminating the need for time averaging and binning.

VivaQuant, LLC  
QA by: __________________________  Date: _____________

### ECG Analysis Services

**Identify arrhythmias, measure intervals, and assess arrhythmia vulnerability.**

MDSP assesses the likelihood that an accurate mark can be identified, just as an operator would during review. If there is too much noise present to be confident, as in this T-wave offset, it avoids placing a mark.

Arrhythmia incidence by hour by type can be reported.
The technology behind MDSP’s exceptional performance

MDSP mitigates the shortcomings of traditional ECG analysis techniques by removing noise without distorting ECG morphology. This is accomplished by dividing the cardiac cycle into two windows – a first window surrounding the QRS complex and a second window that includes the remainder of the cardiac cycle. Since the information content in the QRS complex is quite different than the information contained in the remainder of the cardiac cycle, spatially selective filtering is applied to remove noise. Traditional filtering techniques are unable to take advantage of this due to the trade-offs between time and frequency resolution imposed by the Heisenberg uncertainty principle. This results in “smearing” of information between the two windows where the character of the signal changes rapidly. MDSP circumvents the Heisenberg limitation by decomposing the ECG into multiple mathematical domains with each domain containing a different characteristic of the signal. Domains containing noise are discarded and the ECG signal is then reconstructed from the remaining domains, free of distortion. Five patents have issued and 10 more are pending on this new MDSP technology.

Dynamic QT Beat-to-beat and Restitution Analyses

Dynamic QT beat-to-beat (QTbtb) analysis can circumvent many of the limitations of QTc as a biomarker of arrhythmia vulnerability. QTbtb has been shown to differentiate changes in QT interval duration due to heart rate or autonomic state from impaired repolarization. Dynamic QTbtb analysis compares QT intervals to individual cardiac cycles from all normal autonomic states at similar RR intervals, thereby eliminating potential sources of error from the use of QT correction functions. Since QTbtb compares all treatment related beats to similar beats under all baseline autonomic conditions, it can identify when abnormal autonomic states or impaired repolarization exist that may lead to increased arrhythmia vulnerability. However, under these same conditions, QTc breaks down as a cardiac risk biomarker and can produce either a false positive or false negative indication of cardiac risk. FDA recognizes this limitation of QTc and has initiated an effort with the Cardiovascular Safety Research Consortium to identify alternative techniques that circumvent these limitations. Restitution is a second beat-to-beat analysis tool that can be applied to the same dataset for quantifying the cardiac stress leading to arrhythmia vulnerability. Restitution assesses the ability of the heart to recover from one beat to the next. The methodology measures changes in QT interval (working phase of heart) in response to each preceding TQ interval (resting phase of heart) at every heart rate (RR interval) to quantify the stress on the heart and identify conditions where the likelihood of a re-entry arrhythmia is increased.

MDSP™ Technology Provides Unparalleled Accuracy for Ambulatory ECGs

VivaQuant analysis services employ unique patented MDSP technology to provide accurate and consistent information from noisy ambulatory ECGs. MDSP has been shown to remove 95% of in-band noise (noise that overlaps with ECG spectrum), provide very high accuracy arrhythmia detection, and very low interval measurement variability. MDSP is one of the most significant advances in ECG data processing technology since the Pan-Tomkins technique and template matching/pattern recognition were introduced about 30 years ago. Template-based algorithms work well when analyzing stable, noise-free, and uniform ECGs from sedentary subjects. When noise is present or morphology changes occur, a large number of templates may be needed, leading to erroneous template switching and interval measurement jitter. Conventional approaches require a large number of user-defined configuration parameters that vary from one recording to the next and lead to operator dependent findings. MDSP eliminates these restrictions and requires only that the species and sampling rate be entered.

Interval measurements are carefully reviewed using proprietary software to assure the best possible accuracy.
**QT Beat-to-beat Analysis**

**Features**
- Assesses QT interval changes without use of correction factors by comparing beats at similar heart rates under all normal autonomic conditions and hysteresis.
- Differentiates normal from impaired repolarization at any heart rate not possible with QTc.
- Generates beat-to-beat QT-RR interval plots or “clouds” that allow visual validation and easy interpretation of findings.
- Retrospective analysis possible with continuous ECG data obtained over 20 hours or longer.
- Clinically validated outcomes and used in FDA regulatory facing studies.
- More than 15 years of clinical and preclinical supporting data.

**Benefits**
- Data meets all requirements for ICH E14 Thorough QT assessment and S7B requirements for regulatory filing.
- Fully translational methodology from preclinical (dog or monkey) to clinical data.
- Assesses changes in QT interval during varying autonomic states where QTc can cause false positive/negative indications of arrhythmia liability.
- Data more accurate for PK/PD modeling since not affected by varying autonomic states.
- Provides mechanistic information underlying changes in QT-RR interval relationship.

The table below provides a high-level comparison of how QTc and beat-to-beat analyses respond to various physiological conditions.

<table>
<thead>
<tr>
<th>Drug-induced effect</th>
<th>QTc</th>
<th>Dynamic QT beat-to-beat and ECG restitution analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in autonomic tone</td>
<td>Can produce false positive and false negative interpretations of arrhythmia liability</td>
<td>Quantifies changes in QT interval during all normal autonomic states</td>
</tr>
<tr>
<td>Drug-induced ion channel effects</td>
<td>Quantifies static impact of ion channel effects.</td>
<td>Quantifies dynamic impact of ion channel effects. Provides for evaluation of heterogeneity of repolarization.</td>
</tr>
<tr>
<td>Drug-induced change in heart rate</td>
<td>Works well when characterized within the range of heart rates at baseline.</td>
<td>No dependence on heart rate change since method compares only to beats at the same RR interval. Can evaluate arrhythmia vulnerability for drugs by examining QT/TQ ratio at any heart rate.</td>
</tr>
<tr>
<td>Temporal heterogeneity</td>
<td>Since QTc involves time averaging, temporal heterogeneity is obfuscated.</td>
<td>Can assess the degree of temporal heterogeneity by examining beat-to-beat variability in relationship to upper reference boundaries obtained at baseline.</td>
</tr>
<tr>
<td>Hysteresis</td>
<td>Since QTc involves time averaging, hysteresis effect is obfuscated or corrected for by a second correction method</td>
<td>Fully evaluated as an integral part of the beat-to-beat analyses.</td>
</tr>
</tbody>
</table>

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4. www.cardiac-safety.org
How does it work?

**Step 1:** Continuous ECG recordings are collected (Holter or telemetry) over at least 20 hours prior to and during study periods from any preclinical (canine or primate) or clinical study.

**Step 2:** Digital recordings are processed by VivaQuant’s proprietary Multi-Domain signal Processing (MDSP) and results are tabulated for beat-to-beat analyses by assessing specific parameters related to each QT and preceding RR and TQ interval.

**Step 3:** Baseline relationship of all QT, RR and TQ intervals along with 95% reference bounds created from predose dataset.

**Step 4:** All treatment ECG data are then compared to this relationship on a beat-to-beat basis at the same heart rate to determine magnitude and heterogeneity of dynamic measures.

What is calculated and what does it mean?

- **Median TQ interval:** As relative refractory period approaches zero, arrhythmia vulnerability may increase due to reentry.
- **Lower 5% TQ quantile:** Least amount of rest the most extreme beats are getting. Good indicator of temporal heterogeneity.
- **Median QT/TQ ratio:** A general indicator if restitution is moving toward impairment or stability. The lower the ratio the better.
- **% of beats with QT/TQ ratio > 1:** If higher % of beats is greater than 1 then heart is working more than resting and is under more stress and prone to arrhythmia.
- **Upper 98% quantile of QT/TQ ratio:** The most extreme beats of the heart. The higher this ratio the greater likelihood of triggering an arrhythmia. Good indicator of temporal heterogeneity.

Figure 1: QT beat-to-beat (left side) and ECG restitution (right side) analyses in the same dog from a cross-over design study. QT prolongation with no change in restitution (i.e. drug safe with no increased risk of arrhythmia).

Figure 2: QT beat-to-beat and ECG restitution analysis in the same dog from a cross-over design study. QT prolongation with impaired restitution (i.e. drug has increased risk of arrhythmia).