



Introduction to Therapeutic Area Data Standards User Guide for QT Studies (TAUG-QT)

David Ju
ERT Inc.

PharmaSUG China 2017

Disclaimer

The information in this presentation was compiled from sources believed to be reliable for informational purposes and the presentation reflects the views of the author only.

CONFIDENCE AT EVERY TURN



TRIAL OVERSIGHT

SITE OPTIMIZATION

PATIENT ENGAGEMENT

SAFETY & EFFICACY

CONFIDENCE AT EVERY TURN

Remove uncertainty and risk from your clinical research to move ahead quickly – with confidence

[LEARN MORE](#)

50%+

OF ALL FDA-APPROVED
DRUGS SUPPORTED BY
ERT OVER PAST 4 YEARS

Section 1: TAUG-QT Introduction

Note to readers

- ▶ This is the **provisional** version of the Therapeutic Area Data Standards User Guide for QT Studies.
- ▶ Source Documents:
 - SDTM v1.4, SDTMIG v3.2, and SDTMIG-MDv1.0
 - ADaM v2.1 and ADaMIG v1.0.
 - Supplementary material includes an expanded domain model, a draft domain model, and a draft relationships dataset specification.

Who made this guide?

- ▶ CFAST* QT Studies Team
 - Critical Path Institute
 - Association of Clinical Research Organizations
 - Innovative Medicines Initiative
 - National Cancer Institute – Enterprise Vocabulary Services
 - TransCelerate BioPharma Inc.
 - U.S. Food and Drug Administration

* The Coalition For Accelerating Standards and Therapies

Source: <https://www.cdisc.org/partnerships/cfast>

What does FDA say?

- ▶ TA standards are not data standards
 - rather extend the CDISC foundational standards (e.g., SDTM and ADaM) to represent data that pertains to specific disease areas.
- ▶ TAUGs should not be interpreted as FDA guidance.
- ▶ Sponsors may use new TA extensions
 - not required until the extensions have been incorporated into a SDTMIG version supported by FDA (the supported SDTMIGs are listed in the Data Standards Catalog).
- ▶ The TA extensions that are currently incorporated into FDA supported CDISC foundational standards include QT and 10 other areas

Why TAUG-QT is unique?

- ▶ Other CDISC therapeutic area user guides:
 - categorize the concepts covered into subject/disease characteristics, disease assessments, and routinely collected data
- ▶ TAUG-QT:
 - associated with drug safety
 - (as opposed to, associated with a particular disease or condition to be treated)
- ▶ ICH Efficacy (E) 14 Guidance for Industry
 - E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (May 2005)
 - associated Question and Answers (R1 and R2) documents (May 2012 and March 2014, respectively)

CONTENTS

- ▶ Introduction
- ▶ ECG Overview
- ▶ Summary of Approaches to Studying QT/QTc in Clinical Studies
- ▶ The Thorough QT (TQT) Study
- ▶ Trial Design
- ▶ Subject Characteristics and Eligibility
- ▶ Study Assessments
- ▶ Statistical Analysis

Electrocardiogram Waveform

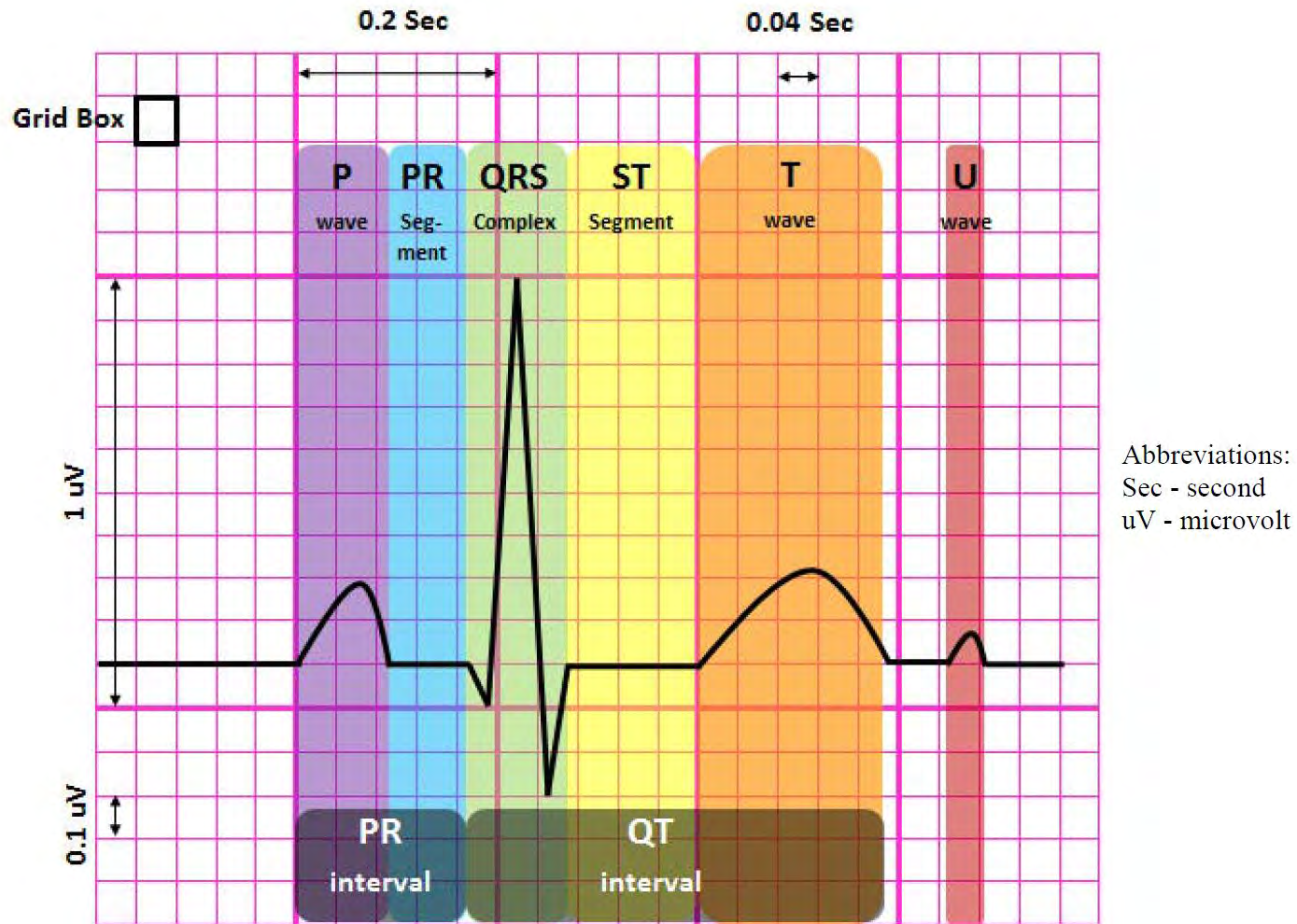


Figure 5: Electrocardiogram Waveform Illustration

Electrocardiogram recorded on grid paper with lines 1mm apart. X-axis is the time axis. Y-axis is the voltage axis. Figure assumes a paper speed of 25mm/sec and a calibration of 10mm/uV.

Section 2: Begin with the End in Mind Focus on Chapter 8

Comparison of QT/QTc

- ▶ PhUSE Analysis and Display White Papers Project Team published “Analyses and Displays Associated with Thorough QT/QTc Studies”
 - provides recommended analyses and displays for common measurements
 - proposes the two following hypothesis tests to perform on TQT/QTc studies:
 - 1. The hypothesis test to confirm no study drug effect that results in a relevant prolongation of the QT/QTc as compared to the placebo group;
 - 2. The study is capable of detecting differences in QT/QTc, (to establish the assay sensitivity) by demonstrating the QT/QTc effects of an active control that results in QTc prolongation only slightly longer than can be observed by chance with placebo (5 to 10 msec range, ideally) can be detected.

ADEG

Row	AVISIT	ATPT	ADT	ATM	EGREPNUM	AVAL	DTYPE	ABLFL	BASE	CHG	ECGPCFL	EGSEQ	EGLEAD	EGREFID	QTCCIFL
1	DAY -1	1 HR	3/22/2014	10:00:21	1	440						4	LEAD II	1234933	Y
2	DAY -1	1 HR	3/22/2014	10:01:35	2	389						8	LEAD II	1289032	Y
3	DAY -1	1 HR	3/22/2014	10:02:14	3	377						12	LEAD II	1343131	Y
4	DAY -1	1 HR	3/22/2014			402	AVERAGE	Y	402						Y
5	DAY -1	2 HR	3/22/2014	11:00:21	1	379						16	LEAD II	1342003	Y
6	DAY -1	2 HR	3/22/2014	11:01:31	2	402						20	LEAD II	1340323	Y
7	DAY -1	2 HR	3/22/2014	11:02:40	3	356						24	LEAD II	1343459	Y
8	DAY -1	2 HR	3/22/2014			379	AVERAGE	Y	379						Y
Additional records for 3 HR, 4 HR, etc...															
9	DAY -1	24 HR	3/23/2014	9:00:07	1	386						100	LEAD II	1347893	Y
10	DAY -1	24 HR	3/23/2014	9:01:38	2	387						104	LEAD V	1348832	Y
11	DAY -1	24 HR	3/23/2014	9:02:34	3	388						108	LEAD II	1348814	Y
12	DAY -1	24 HR	3/23/2014			387	AVERAGE	Y	387						Y
13	DAY 1	1 HR	3/23/2014	10:01:33	1	397						112	LEAD II	1234933	
14	DAY 1	1 HR	3/23/2014	10:02:35	2	403						116	LEAD II	1289032	
15	DAY 1	1 HR	3/23/2014	10:03:34	3	377						120	LEAD II	1343131	
16	DAY 1	1 HR	3/23/2014			392	AVERAGE		402	-10	Y				

- ▶ ADaM Basic Data Structure (BDS).
- ▶ Key variables: STUDYID, USUBJID, PARAMCD, APERIOD, AVISITN, ATPTN, ADT, ATM
- ▶ ADEG.sas: a SAS program in which ADEG has been generated (EG and ADSL)

ADQT

Row	STUDYID	USUBJID	PARAMCD	PARAM	AVAL	AVALC	AGRPID
1	STUDY01	2324-P0001	QTCDESC	QT Correction Method Description		LINEAR	QTCIAG1
2	STUDY01	2324-P0001	QTCFORM	QT Correction Formula		$QTC=QT+(QTCCOEFA*(1-RR))$	QTCIAG1
3	STUDY01	2324-P0001	QTCCOEFA	QT Correction Coefficient A	0.266		QTCIAG1
4	STUDY01	2324-P0001	QTCDESC	QT Correction Method Description		PARABOLIC	QTCIAG2
5	STUDY01	2324-P0001	QTCFORM	QT Correction Formula		$QTC=QT/(RR^{QTCCOEFA})$	QTCIAG2
6	STUDY01	2324-P0001	QTCCOEFA	QT Correction Coefficient A	0.532		QTCIAG2
7	STUDY01	2324-P0001	QTCDESC	QT Correction Method Description		RAUTAHARJU COR	QTCNAG
8	STUDY01	2324-P0001	QTCFORM	QT Correction Formula		$QTC=QT+QTCCOEFA-(QTCCOEFB*(e^{(QTCCOEFC*HR)}))$	QTCNAG
9	STUDY01	2324-P0001	QTCCOEFA	QT Correction Coefficient A	0.2425		QTCNAG
10	STUDY01	2324-P0001	QTCCOEFB	QT Correction Coefficient B	0.434		QTCNAG
11	STUDY01	2324-P0001	QTCCOEFC	QT Correction Coefficient C	-0.0097		QTCNAG
12	STUDY01	2324-P0002	QTCDESC	QT Correction Method Description		LOGARITHMIC	QTCIAG1
13	STUDY01	2324-P0002	QTCFORM	QT Correction Formula		$QTC=QT-QTCCOEFA*\ln(RR)$	QTCIAG1
14	STUDY01	2324-P0002	QTCCOEFA	QT Correction Coefficient A	0.116		QTCIAG1
15	STUDY01	2324-P0002	QTCDESC	QT Correction Method Description		LINEAR	QTCIAG2
16	STUDY01	2324-P0002	QTCFORM	QT Correction Formula		$QTC=QT+(QTCCOEFA*(1-RR))$	QTCIAG2
17	STUDY01	2324-P0002	QTCCOEFA	QT Correction Coefficient A	0.387		QTCIAG2
18	STUDY01	2324-P0002	QTCDESC	QT Correction Method Description		RAUTAHARJU COR	QTCNAG
19	STUDY01	2324-P0002	QTCFORM	QT Correction Formula		$QTC=QT+QTCCOEFA-(QTCCOEFB*(e^{(QTCCOEFC*HR)}))$	QTCNAG
20	STUDY01	2324-P0002	QTCCOEFA	QT Correction Coefficient A	0.2425		QTCNAG
21	STUDY01	2324-P0002	QTCCOEFB	QT Correction Coefficient B	0.434		QTCNAG
22	STUDY01	2324-P0002	QTCCOEFC	QT Correction Coefficient C	-0.0097		QTCNAG

- ▶ ADaM Basic Data Structure (BDS).
- ▶ Key variables: STUDYID, USUBJID, AGRPID, PARAMCD
- ▶ ADQT.sas is a SAS program in which ADQT has been generated; ADQT will mainly have come from QT if it exists

Time-Matched Baseline

Row	USUBJID	TRTP	PARAMCD	APERIOD	AVISIT	ATPT	EGREPNUM	AVAL	DTYPE	ABLFL	BASE	CHG	BASETYPE
1	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR	1	387	}				PERIOD 1, TIME-MATCH 1 HR
2	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR	2	357					PERIOD 1, TIME-MATCH 1 HR
3	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR	3	364					PERIOD 1, TIME-MATCH 1 HR
4	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR		369	AVERAGE	Y	369		PERIOD 1, TIME-MATCH 1 HR
5	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR	1	361	}				PERIOD 1, TIME-MATCH 2 HR
6	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR	2	376					PERIOD 1, TIME-MATCH 2 HR
7	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR	3	409					PERIOD 1, TIME-MATCH 2 HR
8	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR		382	AVERAGE	Y	382		PERIOD 1, TIME-MATCH 2 HR
Additional records for 3 HR, 4 HR, etc...													
9	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR	1	400	}				PERIOD 1, TIME-MATCH 1 HR
10	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR	2	388					PERIOD 1, TIME-MATCH 1 HR
11	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR	3	379					PERIOD 1, TIME-MATCH 1 HR
12	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR		389	AVERAGE		369	20	PERIOD 1, TIME-MATCH 1 HR
13	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR	1	396	}				PERIOD 1, TIME-MATCH 2 HR
14	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR	2	384					PERIOD 1, TIME-MATCH 2 HR
15	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR	3	402					PERIOD 1, TIME-MATCH 2 HR
16	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR		394	AVERAGE		382	12	PERIOD 1, TIME-MATCH 2 HR

Time-Averaged Baseline

Row	USUBJID	TRTP	PARAMCD	APERIOD	AVISIT	ATPT	EGREPNUM	AVAL	DTYPE	ABLFL	BASE	CHG	BASETYPE
1	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR	1	387	}				PERIOD 1, TIME-AVG
2	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR	2	357					PERIOD 1, TIME-AVG
3	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR	3	364					PERIOD 1, TIME-AVG
4	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	1 HR		369	AVERAGE				PERIOD 1, TIME-AVG
5	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR	1	361	}				PERIOD 1, TIME-AVG
6	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR	2	376					PERIOD 1, TIME-AVG
7	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR	3	409					PERIOD 1, TIME-AVG
8	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	2 HR		382	AVERAGE				PERIOD 1, TIME-AVG
3 HR, 4 HR, 6 HR, 8 HR, 10 HR, 12 HR, and 24 HR replicate averages (not shown)													
9	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY -1	LINE		370	AVERAGE	Y	370		PERIOD 1, TIME-AVG
10	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR	1	400					PERIOD 1, TIME-AVG
11	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR	2	388					PERIOD 1, TIME-AVG
12	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR	3	379					PERIOD 1, TIME-AVG
13	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	1 HR		389	AVERAGE		370	19	PERIOD 1, TIME-AVG
14	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR	1	396					PERIOD 1, TIME-AVG
15	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR	2	384					PERIOD 1, TIME-AVG
16	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR	3	402					PERIOD 1, TIME-AVG
17	2324-P0001	Drug A 1 mg	QTCFAG	1	DAY 1	2 HR		394	AVERAGE		370	24	PERIOD 1, TIME-AVG

Section 3: PhUSE Guide Outputs (TLFs)

PhUSE:

► Analyses and Displays Associated with Thorough QT/QTc Studies

Type	Title
Figure	Box plots of change from baseline in continuous ECG parameters by time-point for each treatment
Figure	Estimated mean difference in comparison to placebo and 90% CI for change from baseline in QTc ($\Delta\Delta\text{QTc}$) for treatment
Figure	Estimated mean difference in comparison to placebo and 90% CI for change from baseline in QTc ($\Delta\Delta\text{QTc}$) for active control
Figure	Raw mean (+/-SE) change from baseline in continuous ECG parameters by treatment
Figure	Concentration response for change from baseline in QTc for active control (assay-sensitivity)
Figure	Concentration response for change from baseline in QTc for treatment
Table	Treatment comparisons of change from baseline in QTc intervals by time for treatment
Table	Treatment comparisons of change from baseline in QTc intervals by time for active control
Table	Treatment comparisons of change from baseline to all time points in ECG parameters (HR, PR, QRS) by time for treatment
Table	Summary of values and changes from baseline to all time points in ECG parameters by time and treatment
Table	Number and percentage of subjects meeting or exceeding clinically noteworthy QT and QTc interval changes by time point and overall
Table	Number and percentage of subjects meeting or exceeding clinically noteworthy PR, QRS and HR interval changes by time point and overall
Table	Number and percentage of subjects with abnormal morphological/qualitative ECG findings
Listing	ECG intervals (average over repeated measurements)
Listing	Change from baseline in ECG intervals (average over repeated measurements)
Listing	ECG intervals (each replicate)
Listing	ST segment, T-wave and U-wave morphology
Listing	ECG findings

Section 4: Tips / Demo

A Quick Development of Figures

SAS studio

▶ Box Plot

- Tasks > Graph > Box Plot
- Creates codes
- Run the program and review results

▶ Snippets

- SAS programmers can also prepare the template programs of figures
- Save them snippets
- Open the program and change parameters
- Run the program and review results

Box Plot

The screenshot displays the SAS Studio interface with the 'Box Plot' task selected in the 'Tasks and Utilities' pane. The configuration pane shows the following settings:

- DATA:** _TEMPO.ADEG
- WHERE CLAUSE FILTER:**
- ROLES:**
 - Analysis variable:** CHG
 - Category variable:** ATPT
 - Group variable:** TRTP
 - BY variable:** PARAMCD
- DIRECTION:**

The code pane shows the SAS program for generating the box plot:

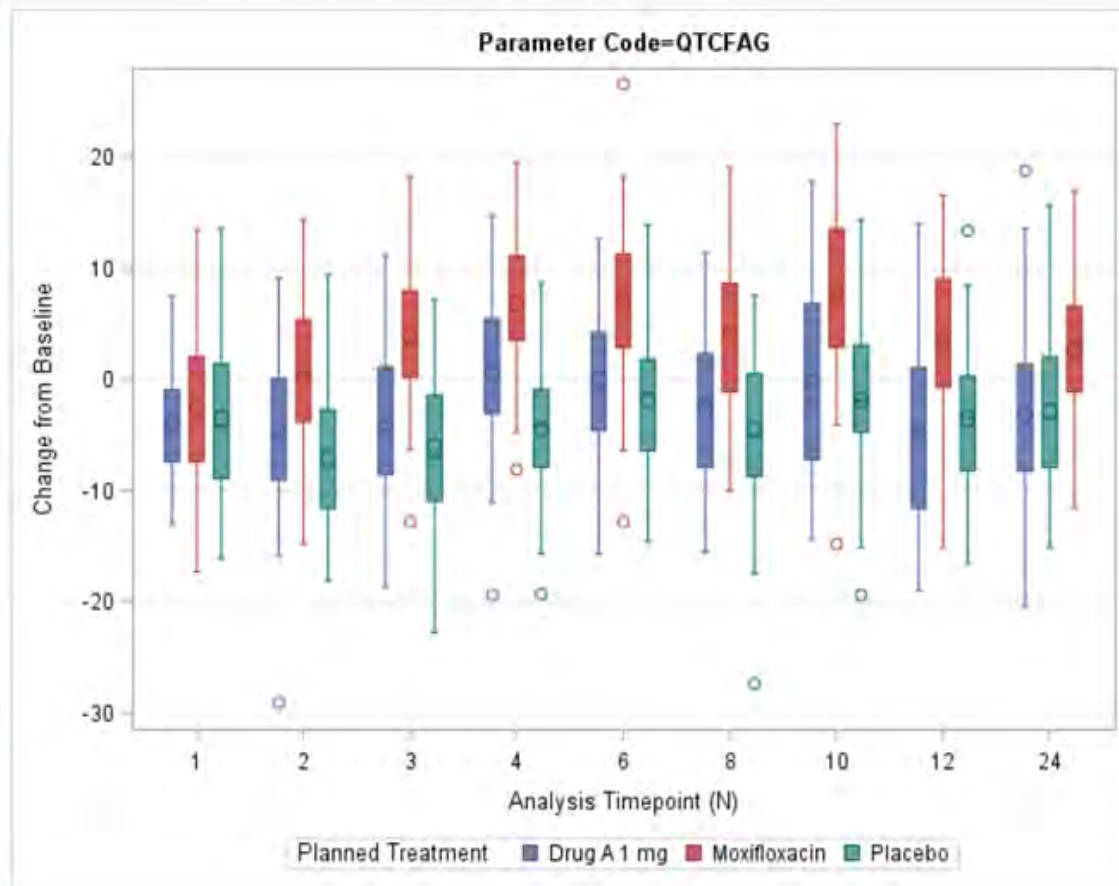
```
1 /*  
2 *  
3 * Task code generated by SAS Studio 3.5  
4 *  
5 * Generated on '6/6/17. 8:25 PM'  
6 * Generated by '  
7 * Generated on server  
8 * Generated on SAS platform 'X64_8PRO_WIN'  
9 * Generated on SAS version '9.04.01M3P06242015'  
10 * Generated on browser 'Mozilla/5.0 (Windows NT 10.0; Win  
11 * Generated on web client 'http://  
12 *  
13 */  
14  
15 /*--Sort data by BY variable--*/  
16 proc sort data= ' _TEMPO.ADEG out= _BoxPlotTaskData;  
17     by PARAMCD;  
18 run;  
19  
20 /*--Set output size--*/  
21 ods graphics / reset imagemap;  
22  
23 /*--SGPLOT proc statement--*/  
24 proc sgplot data= BoxPlotTaskData;  
25     /*--BY Variable--*/  
26     by PARAMCD;  
27  
28     /*--TITLE and FOOTNOTE--*/  
29     /*--Box Plot settings--*/  
30     vbox CHG / category=ATPT group=TRTP grouporder=Data  
31  
32     /*--Category Axis--*/  
33     xaxis fitpolicy=splitrotate;  
34  
35     /*--Response Axis--*/  
36     yaxis grid;  
37
```

Box Plot

Find on page atpt

No results

< > Options v



Snippets

SAS® Studio

Files and Folders

Tasks and Utilities

Snippets

- My Snippets
 - boxplot
 - Tmp Change from Baseline
- Snippets

Libraries

File Shortcuts

Tmp Change from Baseline

CODE LOG RESULTS OUTPUT DATA

Table of Contents

PROTOCOL/PRODUCT INFO: (page x of x)
Raw mean (+/-SE) change from baseline in continuous ECG parameters by treatment
Analysis set: PD analysis set

Cardiac parameter:
Treatment:

time(unit)	Active (msec)	Placebo (msec)
0	-1.5	1.0
1	-0.5	0.5
2	2.5	0.5
4	2.5	2.5
8	1.5	1.5
12	-1.5	0.0
16	-0.5	-0.5
20	-1.0	-1.0
24	0.0	-1.5

Median Change (msec)

time(unit)

Active Placebo

PATH DATA/PROGRAM/OUTPUT
PRODUCTION STATUS/RUN DDMMYYYY HHMM

Other tips

- ▶ Quality is critical: even a few milliseconds matter
- ▶ Study design is a science: borrow brains
- ▶ QTc calculation

Concluding Thoughts

- ▶ Regulatory agencies around the globe may not share the same opinions or statuses on adopting CDISC for submission and review
 - consult with the intended regulatory agency to confirm the requirements when planning trial
- ▶ Get involved and join CDISC as a member:
<http://cdisc.org/register>
- ▶ Submit comments in public reviews
- ▶ Participate in a working group

Questions?



Author Contact Information

Name: David Ju

Organization: ERT Inc.

Address: 1818 Market Street, Suite 1000

City, State ZIP: Philadelphia, PA 19103

Work Phone: +1 215-972-0420

Fax: +1 215-972-8133

E-mail: dju@ert.com

Web: www.ert.com

References

- ▶ N/A. (2013). CDISC SDTM Implementation Guide (Version 3.2). N/A: Clinical Data Interchange Standards Consortium, Inc. Available at <http://www.cdisc.org/sdtm>
- ▶ N/A. (2014). Therapeutic Area Data Standards User Guide for QT Studies Version 1.0 (Provisional). N/A: Clinical Data Interchange Standards Consortium, Inc. Available at <http://www.cdisc.org/sdtm>.
- ▶ N/A. (2016). Analysis Data Model Implementation Guide (Version 1.1). N/A: Clinical Data Interchange Standards Consortium, Inc. Available at <http://www.cdisc.org/sdtm>.
- ▶ N/A. (2016). Analyses and Displays Associated with Thorough QT/QTc Studies. N/A: PhUSE. Available at <http://www.phusewiki.org/docs/CSS%20White%20Papers%202016/>
- ▶ N/A. (2017). STUDY DATA TECHNICAL CONFORMANCE GUIDE. N/A: FDA. Available at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>