Technical Specification for Submitting Data for QT Studies

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Agenda and Goals

- At the end of this webinar you will be able to answer the following questions:
  - What is a technical specifications document?
  - Why do we need a technical specifications document for QT studies?
  - How can I use the technical specifications document for QT studies?

WHAT IS A TECHNICAL SPECIFICATIONS DOCUMENT?

Technical specifications documents

Guidance for Industry
Technical Specifications Document

- Are a means by which the FDA can communicate or clarify a specific data or information submission need, often with a focus on a specific area or discipline
- Build heavily upon standards in the FDA Data Standards Catalog
- Clarify how data from different studies should be organized

The need for a Technical Specification for QT Studies

WHY A TECHNICAL SPECIFICATIONS DOCUMENT FOR QT STUDIES?

Evolution of clinical QT assessment

- Clinical assessment of drug-induced QT prolongation and proarrhythmic potential is required for almost all new drugs since 2005
- Typically done in a single dedicated thorough QT (TQT) study as described in ICH E14
- On December 2015, ICH E14 Q&A R3 enabled concentration-response analysis to be used as primary analysis in QT studies

Impact of concentration-response

- Allows the use drug concentration (PK) and QT data gathered outside dedicated TQT studies as substitute for a TQT study
- Speeds up and reduces costs of drug development programs by enabling use of first in human data or pooling data across studies
- Increases the heterogeneity of QT study designs

Existing data standards

- SDTM, ADaM, and a Therapeutic Area User Guide for QT Studies (TAUG-QT) developed by the CDISC are already available
- The TAUG-QT provides a harmonized standard for QT study data, but
  - still requires ad-hoc data wrangling to produce an analysis-ready dataset for typical QT analyses
  - its flexibility often requires custom data manipulation code to obtain the analysis-ready dataset
  - PK datasets (i.e., PC domain) are not covered → inconsistencies/mismatches between PC, EG, and ADEG

Data challenges

- Heterogeneity in study designs is not an issue for collection and analysis of drug concentration (PK) and QT data for a given study
- But data management and analysis challenges arise
  - At study level when PK and QT datasets were put together by different sub-teams
  - When pooling data from multiple studies
  - Inconsistencies in naming, coding and definitions:
    - e.g., treatments, dosing, nominal timepoints, and/or baseline
- Efficiently addressing these challenges becomes critical when reviewing and analyzing large number of QT studies from multiple therapeutic areas

Why a technical specification for QT?

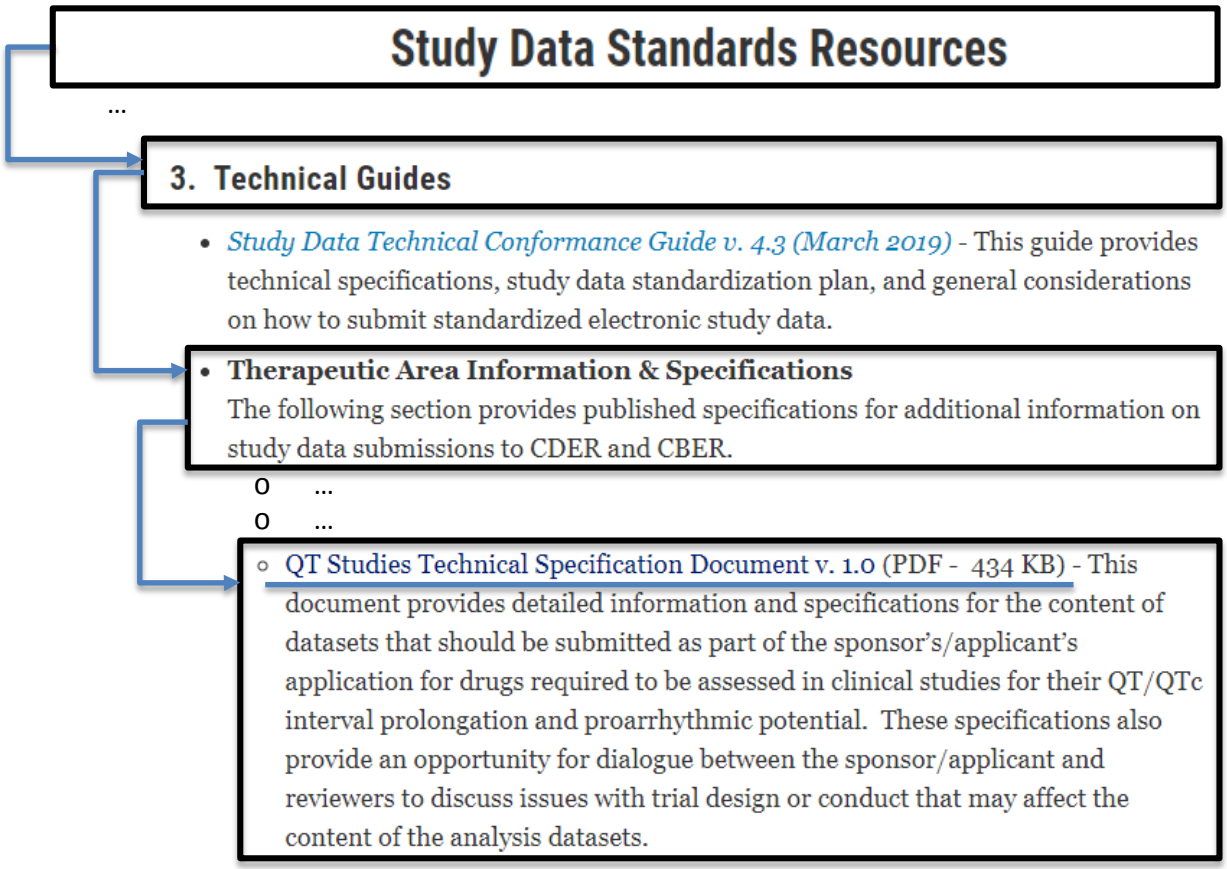
- To address the challenges associated with the increased heterogeneity in study designs, provide clarity on structure, terminology, and linkage for QT study data that will streamline the review and analysis of QT datasets

HOW TO USE THE TECHNICAL SPECIFICATIONS DOCUMENT FOR QT STUDIES?

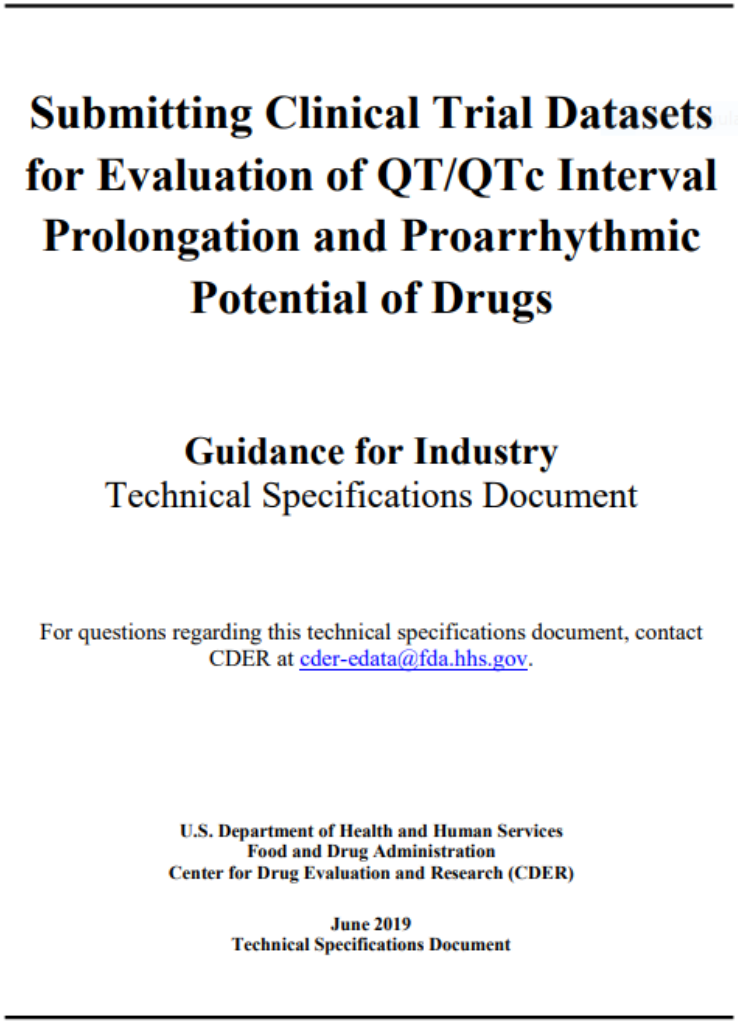
Technical Specifications for QT

- FDA's Study Data Standards Resources webpage

https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources



Technical specifications for QT



Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs

Guidance for Industry
Technical Specifications Document

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2019
Technical Specifications Document

Describes three analysis datasets

- ADSL
  - subject level information
- ADEG
  - QT and other ECG parameters
  - e.g., HR, PR, QRS
- ADPC:
  - drug concentration (pharmacokinetic [PK]) data

Use cases

- Next slides provide details about the examples included in the Technical Specifications for QT

- Use case examples
  - Time encoding
  - Baseline encoding
  - Encoding and computing changes from placebo
  - ADPC and ADEG including both time-matched and additional timepoints for PK and ECG data
  - Use of analysis flags
  - Coding a parallel with nested crossover design

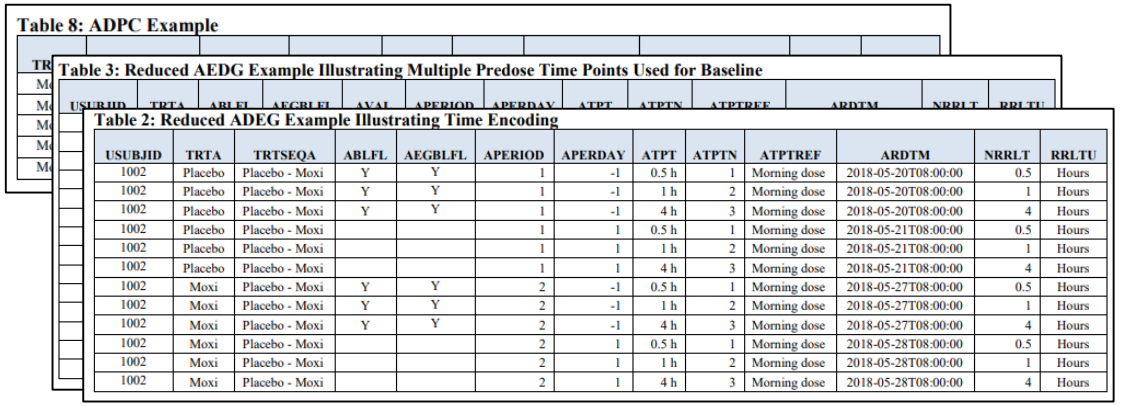


Table 8: ADPC Example

Table 3: Reduced AEDG Example Illustrating Multiple Predose Time Points Used for Baseline

Table 2: Reduced ADEG Example Illustrating Time Encoding

USUBJID	TRTA	TRTSEQA	ABLFL	AEGBLFL	APERIOD	APERDAY	ATPT	ATPTN	ATPTREF	ARDTM	NRRLT	RRLTU
1002	Placebo	Placebo - Moxi	Y	Y	1	-1	0.5 h	1	Morning dose	2018-05-20T08:00:00	0.5	Hours
1002	Placebo	Placebo - Moxi	Y	Y	1	-1	1 h	2	Morning dose	2018-05-20T08:00:00	1	Hours
1002	Placebo	Placebo - Moxi	Y	Y	1	-1	4 h	3	Morning dose	2018-05-20T08:00:00	4	Hours
1002	Placebo	Placebo - Moxi			1	1	0.5 h	1	Morning dose	2018-05-21T08:00:00	0.5	Hours
1002	Placebo	Placebo - Moxi			1	1	1 h	2	Morning dose	2018-05-21T08:00:00	1	Hours
1002	Placebo	Placebo - Moxi			1	1	4 h	3	Morning dose	2018-05-21T08:00:00	4	Hours
1002	Moxi	Placebo - Moxi	Y	Y	2	-1	0.5 h	1	Morning dose	2018-05-27T08:00:00	0.5	Hours
1002	Moxi	Placebo - Moxi	Y	Y	2	-1	1 h	2	Morning dose	2018-05-27T08:00:00	1	Hours
1002	Moxi	Placebo - Moxi	Y	Y	2	-1	4 h	3	Morning dose	2018-05-27T08:00:00	4	Hours
1002	Moxi	Placebo - Moxi			2	1	0.5 h	1	Morning dose	2018-05-28T08:00:00	0.5	Hours
1002	Moxi	Placebo - Moxi			2	1	1 h	2	Morning dose	2018-05-28T08:00:00	1	Hours
1002	Moxi	Placebo - Moxi			2	1	4 h	3	Morning dose	2018-05-28T08:00:00	4	Hours

Time encoding

TRTA	TRTSEQA	ABLFL	AEGBLFL	APERIOD	APERDAY	ATPT	ATPTN	ATPTREF	ARDTM	NRRLT	RRLTU
Pbo	Placebo – Moxi	Y	Y	1	-1	0.5 h	1	Morning dose	2018-05-20T08:00:00	0.5	Hours
Pbo	Placebo – Moxi	Y	Y	1	-1	1 h	2	Morning dose	2018-05-20T08:00:00	1	Hours
Pbo	Placebo - Moxi	Y	Y	1	-1	4 h	3	Morning dose	2018-05-20T08:00:00	4	Hours
Pbo	Placebo - Moxi			1	1	0.5 h	1	Morning dose	2018-05-21T08:00:00	0.5	Hours
Pbo	Placebo - Moxi			1	1	1 h	2	Morning dose	2018-05-21T08:00:00	1	Hours
Pbo	Placebo - Moxi			1	1	4 h	3	Morning dose	2018-05-21T08:00:00	4	Hours
Moxi	Placebo - Moxi	Y	Y	2	-1	0.5 h	1	Morning dose	2018-05-27T08:00:00	0.5	Hours
Moxi	Placebo - Moxi	Y	Y	2	-1	1 h	2	Morning dose	2018-05-27T08:00:00	1	Hours
Moxi	Placebo - Moxi	Y	Y	2	-1	4 h	3	Morning dose	2018-05-27T08:00:00	4	Hours
Moxi	Placebo - Moxi			2	1	0.5 h	1	Morning dose	2018-05-28T08:00:00	0.5	Hours
Moxi	Placebo - Moxi			2	1	1 h	2	Morning dose	2018-05-28T08:00:00	1	Hours
Moxi	Placebo - Moxi			2	1	4 h	3	Morning dose	2018-05-28T08:00:00	4	Hours

Source: QT Studies Technical Specification Document, Table 2: reduced ADEG example for 1 subject

- ATPTN encoded as sequence number.
- NRRLT time in RRLTU (Hours) from ATPTREF (Morning Dose)
- ATPTREF time in ARDTM (i.e., 08:00:00 am on 05/20/2018, 5/21/2018 for APERDAY -1 and 1 during APERIOD 1 and on 05/27/2018 and 05/28/2018 for APERDAY -1 and 1 during APERIOD 2).

Multiple timepoints for baseline

TRTA	ABLFL	AEGBLFL	AVAL	APERIOD	APERDAY	ATPT	ATPTN	ATPTREF	ARDTM	NRRLT	RRLTU
Pbo		Y	381.133	1	1	-1 h	1	Morning dose	2018-05-21T08:00:00	-1	Hours
Pbo		Y	380.066	1	1	-0.5 h	2	Morning dose	2018-05-21T08:00:00	-0.5	Hours
Pbo		Y	380.632	1	1	0 h	3	Morning dose	2018-05-21T08:00:00	0	Hours
Pbo	Y		380.610	1	1	Baseline	4	Morning dose	2018-05-21T08:00:00	0	Hours
Pbo			378.179	1	1	0.5 h	5	Morning dose	2018-05-21T08:00:00	0.5	Hours
Pbo			376.497	1	1	1 h	6	Morning dose	2018-05-21T08:00:00	1	Hours
Pbo			366.803	1	1	4 h	7	Morning dose	2018-05-21T08:00:00	4	Hours
Moxi		Y	395.322	2	1	-1 h	1	Morning dose	2018-05-28T08:00:00	-1	Hours
Moxi		Y	393.478	2	1	-0.5 h	2	Morning dose	2018-05-28T08:00:00	-0.5	Hours
Moxi		Y	392.465	2	1	0 h	3	Morning dose	2018-05-28T08:00:00	0	Hours
Moxi	Y		393.755	2	1	Baseline	4	Morning dose	2018-05-28T08:00:00	0	Hours
Moxi			400.421	2	1	0.5 h	5	Morning dose	2018-05-28T08:00:00	0.5	Hours
Moxi			383.874	2	1	1 h	6	Morning dose	2018-05-28T08:00:00	1	Hours
Moxi			378.260	2	1	4 h	7	Morning dose	2018-05-28T08:00:00	4	Hours

average

average

Source: QT Studies Technical Specification Document, Table 3: reduced ADEG example for 1 subject

- Baseline defined as the average of the 3 timepoints before dosing (i.e., -1, -0.5 and 0 hours)
- AEGBLFL flags the observations needed to compute baseline
- ABLFL flags the (computed) baseline

Time-matched baseline

CHG = AVAL - BASE

USUBJID	APERIOD	APERDAY	ATPTREF	NRRLT	RRLTU	AVAL	EGSTRESU	ABLFL	BASE	CHG	BASETYPE
1002	1	-1	Morning dose	0.5	Hours	372.333	msec	Y	372.333		Baseline Day 0.5 h
1002	1	-1	Morning dose	1	Hours	375.000	msec	Y	375.000		Baseline Day 1 h
1002	1	-1	Morning dose	4	Hours	372.667	msec	Y	372.667		Baseline Day 4 h
1002	1	14	Morning dose	0.5	Hours	374.000	msec		372.333	1.667	Baseline Day 0.5 h
1002	1	14	Morning dose	1	Hours	375.667	msec		375.000	0.667	Baseline Day 1 h
1002	1	14	Morning dose	4	Hours	371.000	msec		372.667	-1.667	Baseline Day 4 h
1003	1	-1	Morning dose	0.5	Hours	402.333	msec	Y	402.333		Baseline Day 0.5 h
1003	1	-1	Morning dose	1	Hours	401.333	msec	Y	401.333		Baseline Day 1 h
1003	1	-1	Morning dose	4	Hours	406.667	msec	Y	406.667		Baseline Day 4 h
1003	1	14	Morning dose	0.5	Hours	393.667	msec		402.333	-8.667	Baseline Day 0.5 h
1003	1	14	Morning dose	1	Hours	397.333	msec		401.333	-4.000	Baseline Day 1 h
1003	1	14	Morning dose	4	Hours	396.667	msec		406.667	-10.000	Baseline Day 4 h

Source: QT Studies Technical Specification Document, Table 4: reduced ADEG example

- BASETYPE can be used as a key (i.e., without parsing) and to describe the baseline definition
- BASE column populated based on BASETYPE match by USUBJID
- CHG = AVAL - BASE

Changes from placebo

CCOMPCHG = CHG- COMPCHG

Parallel study design

USUBJID	TRTA	NRRLT	AVAL	BASE	CHG	ACOMPFL	COMP	COMPBASE	COMPCHG	CCOMPCHG	COMPTYPE
1001	Drug	0.5	390.333	390.333	0.000		388.889	391.111	-2.222	2.222	Placebo group at 0.5 h
1001	Drug	1	388.333	393.333			390.111	393.389	-3.278	-1.722	Placebo group at 1 h
1001	Drug	4	387.333	381.000			388.222	389.556	-1.333	7.667	Placebo group at 4 h
1002	Placebo	0.5	374.000	372.333	1.667	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1002	Placebo	1	375.667	375.000	0.667	Y	390.111	393.389	-3.278		Placebo group at 1 h
1002	Placebo	4	371.000	372.667	-1.667	Y	388.222	389.556	-1.333		Placebo group at 4 h
1003	Placebo	0.5	393.667	402.333	-8.667	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1003	Placebo	1	397.333	401.333	-4.000	Y	390.111	393.389	-3.278		Placebo group at 1 h
1003	Placebo	4	396.667	406.667	-10.000	Y	388.222	389.556	-1.333		Placebo group at 4 h
1005	Placebo	0.5	401.667	392.333	9.333	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1005	Placebo	1	398.333	392.667	5.667	Y	390.111	393.389	-3.278		Placebo group at 1 h
1005	Placebo	4	399.333	390.333	9.000	Y	388.222	389.556	-1.333		Placebo group at 4 h
1007	Placebo	0.5	378.000	383.000	-5.000	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1007	Placebo	1	377.667	390.000	-12.333	Y	390.111	393.389	-3.278		Placebo group at 1 h
1007	Placebo	4	381.000	387.000	-6.000	Y	388.222	389.556	-1.333		Placebo group at 4 h
1008	Placebo	0.5	398.667	410.333	-11.667	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1008	Placebo	1	401.333	412.333	-11.000	Y	390.111	393.389	-3.278		Placebo group at 1 h
1008	Placebo	4	396.000	399.667	-3.667	Y	388.222	389.556	-1.333		Placebo group at 4 h
1010	Placebo	0.5	387.333	386.333	1.000	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1010	Placebo	1	390.333	389.000	1.333	Y	390.111	393.389	-3.278		Placebo group at 1 h
1010	Placebo	4	385.333	381.000	4.333	Y	388.222	389.556	-1.333		Placebo group at 4 h

average

Source: QT Studies Technical Specification Document, Table 5: reduced ADEG example (parallel study design)

- COMPTYPE can be used as a key (i.e., without parsing) and to describe the placebo definition
- COMP and COMPBASE columns populated based on COMPTYPE match
- COMPCHG = COMP – COMPBASE → CCOMPCHG = CHG - COMPCHG

Time encoding consistency between ADEG & ADPC

ADEG

TRTA	TRTSEQA	APERIOD	APERDAY	ECGPCFL	ATPT	ATPTN	ATPTREF	ARDTM	NRRLT	RRLTU
Moxi	Moxi -Placebo	1	1	Y	0.5 h	1	Morning dose	2018-05-21T08:00:00	0.5	Hours
Moxi	Moxi -Placebo	1	1	Y	1 h	2	Morning dose	2018-05-21T08:00:00	1	Hours
Moxi	Moxi -Placebo	1	1	Y	4 h	3	Morning dose	2018-05-21T08:00:00	4	Hours
Moxi	Moxi -Placebo	1	1		12 h	4	Morning dose	2018-05-21T08:00:00	12	Hours
Moxi	Moxi -Placebo	1	1	Y	16 h	6	Morning dose	2018-05-21T08:00:00	16	Hours

Source: QT Studies Technical Specification Document, Table 7: ADEG example

ADPC

TRTA	TRTSEQA	APERIOD	APERDAY	ATPT	ATPTN	ATPTREF	ARDTM	NRRLT	RRLTU
Moxi	Moxi -Placebo	1	1	0.5 h	1	Morning dose	2018-05-21T08:00:00	0.5	Hours
Moxi	Moxi -Placebo	1	1	1 h	2	Morning dose	2018-05-21T08:00:00	1	Hours
Moxi	Moxi -Placebo	1	1	4 h	3	Morning dose	2018-05-21T08:00:00	4	Hours
Moxi	Moxi -Placebo	1	1	14 h	5	Morning dose	2018-05-21T08:00:00	14	Hours
Moxi	Moxi -Placebo	1	1	16 h	6	Morning dose	2018-05-21T08:00:00	16	Hours

Source: QT Studies Technical Specification Document, Table 8: ADPC example

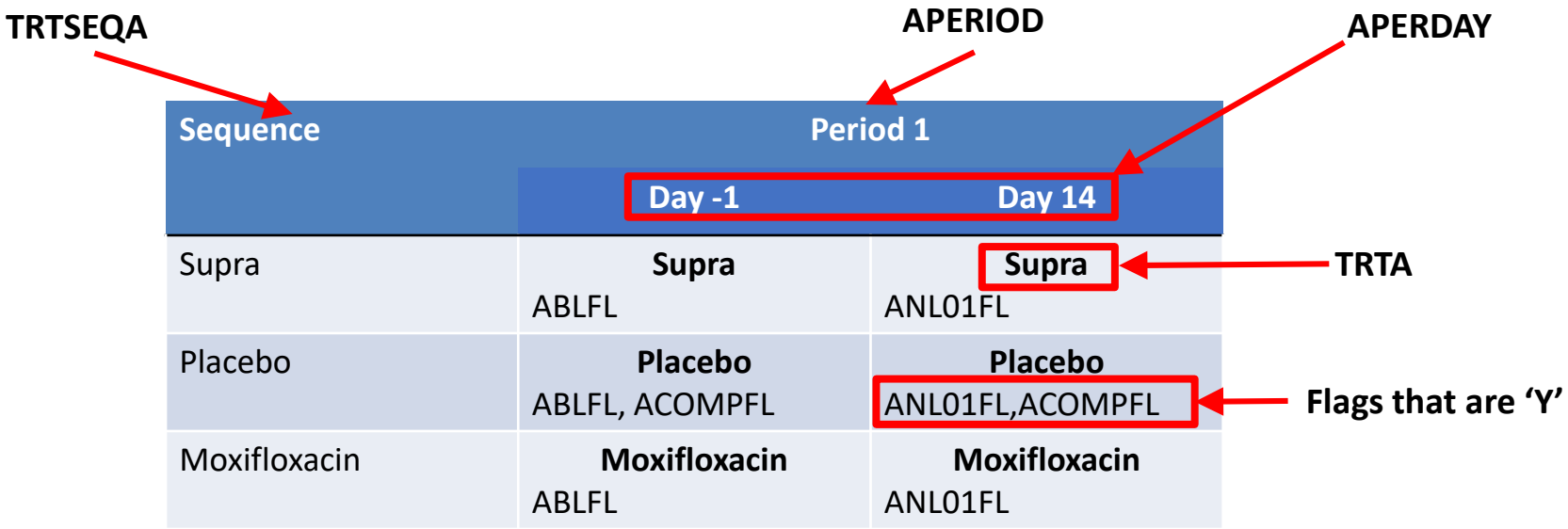
- ATPT and ATPTN are coded consistently between ADEG and ADPC
- ADEG: 12 hours after the morning dose has ECG data that has no PK sample in ADPC
- ADPC: PK sample collected at 14 hours after the morning dose has no ECG data in ADEG

Use of analysis flags

- A set of analysis flags are recommended to facilitate analysis of data from QT studies:
  - ANL01FL: Primary analysis, e.g. rows with ANL01FL='Y' are used in primary analysis
  - ANL02FL: Assay sensitivity, e.g. rows with ANL02FL='Y' are used only for assay sensitivity

Examples

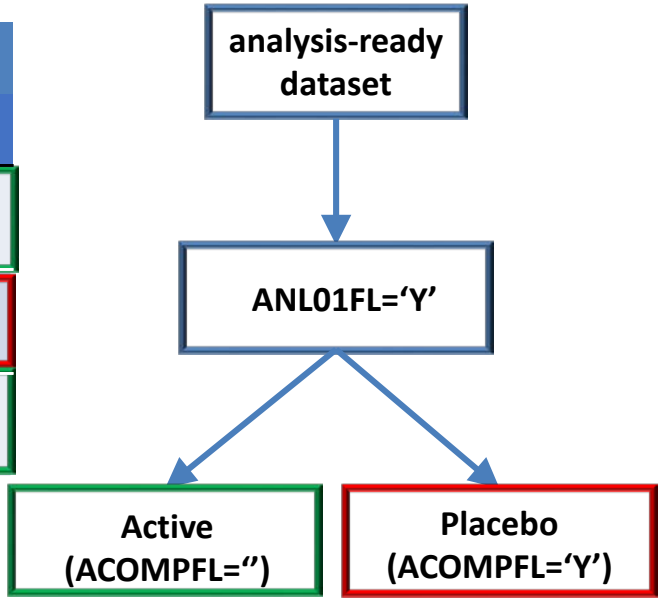
- Following examples focus on use of ANLxxFL and ACOMPFL (i.e., what observations)
- Column names as shown in example below
  - Parallel study with placebo, supra and moxifloxacin with 14 days of dosing



Example 1: Parallel study

- Study used: Placebo, supra and moxifloxacin with 14 days of dosing:

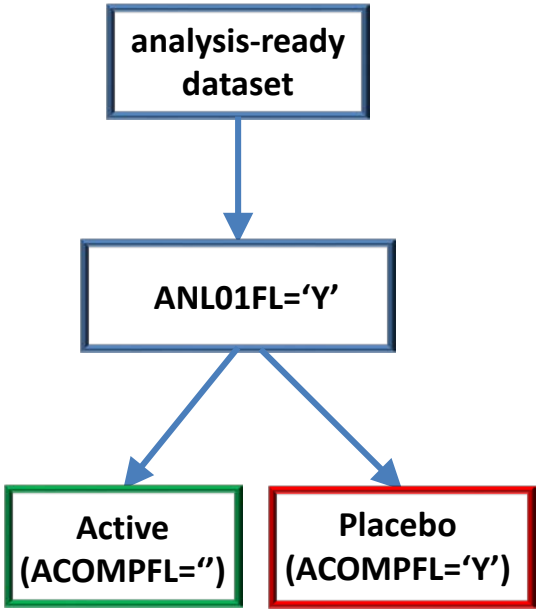
Sequence	P	
	Day -1	Day 14
Supra	**Supra** ABLFL	**Supra** ANL01FL
Placebo	**Placebo** ABLFL, ACOMPFL	**Placebo** ANL01FL,ACOMPFL
Moxifloxacin	**Moxifloxacin** ABLFL	**Moxifloxacin** ANL01FL



Example 2: Cross-over study

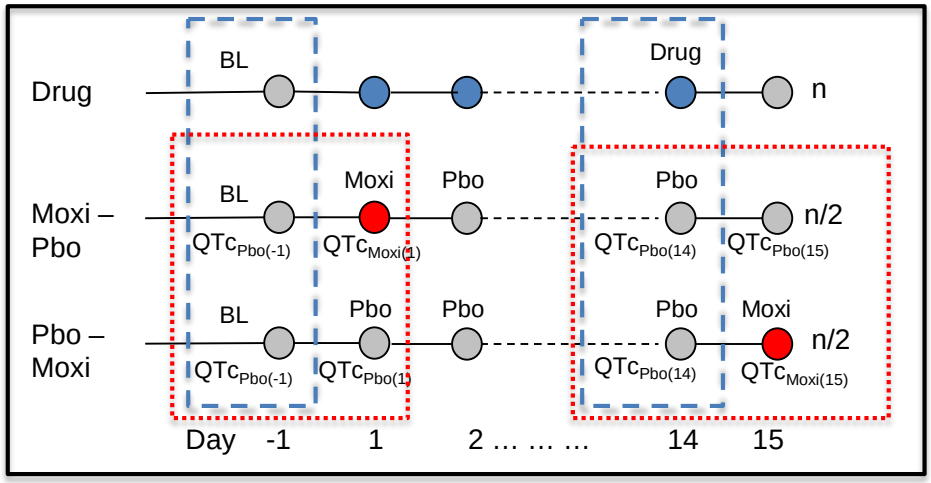
- Study used: 3-way cross-over with supratherapeutic, placebo and moxifloxacin.

Sequence	Period 1	Period 2	Period 3
	Day 1	Day 1	Day 1
Supra-Placebo Moxi	**Supra** ABLFL*, ANL01FL	**Placebo** ABLFL*, ANL01FL, ACOMPFL	**Moxi** ABLFL*, ANL01FL
Supra-Moxi-Placebo	**Supra** ABLFL*, ANL01FL	**Moxi** ABLFL*, ANL01FL	**Placebo** ABLFL*, ANL01FL, ACOMPFL
Placebo-Supr Moxi	**Placebo** ABLFL*, ANL01FL, ACOMPFL	**Supra** ABLFL*, ANL01FL	**Moxi** ABLFL*, ANL01FL



* ABLFL is only true for the pre-dose baseline
** Only showing three sequences to keep the slide simple

Example 3: Parallel study with nested xo



General considerations

- All treatment arms are randomized
- Same number of days from baseline for both the study drug and moxifloxacin
- Same comparisons for both the study drug and moxifloxacin
- ΔΔ for both the study drug and moxifloxacin

Parallel part

ΔΔ for the study drug:

- same as the conventional parallel design
  - Baseline on Day -1
  - Drug effect on Day 14
- Placebo (Pbo) combined data from Moxi-Pbo and Pbo-Moxi arms

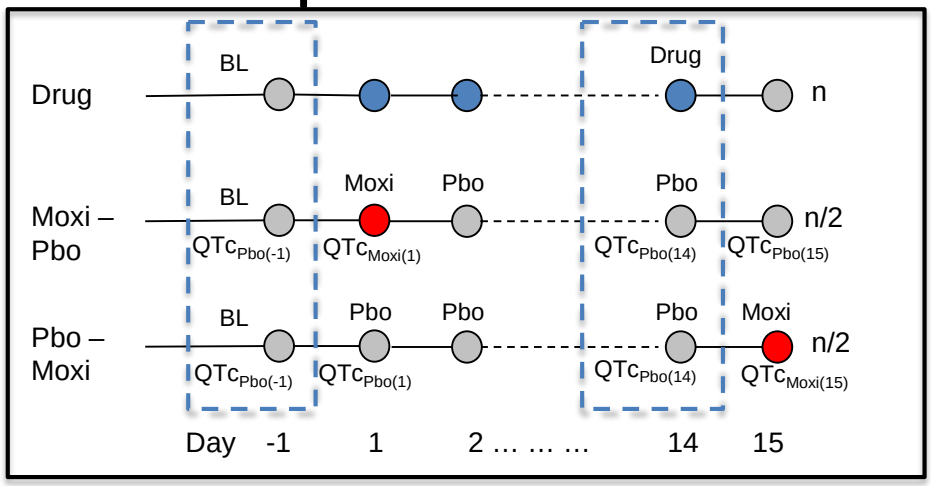
Nested crossover part

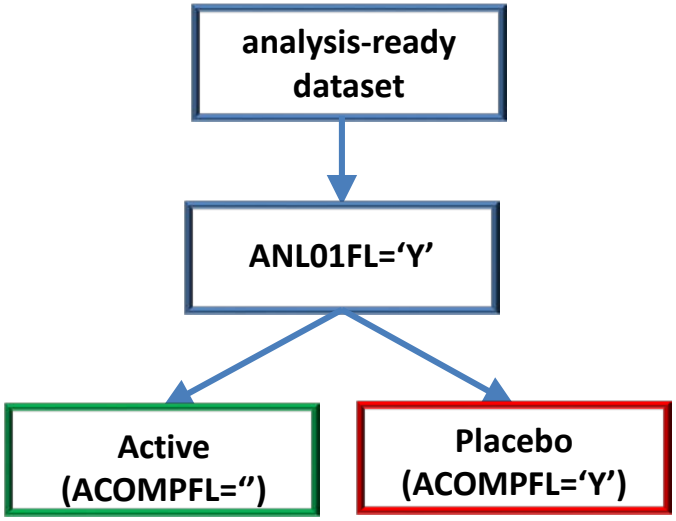
ΔΔ for moxifloxacin (moxi)

- Moxi-Pbo: $[QTc_{Moxi}(1) - QTc_{Pbo}(15)] - [QTc_{Pbo}(14) - QTc_{Pbo}(-1)]$
- Pbo-Moxi: $[QTc_{Moxi}(15) - QTc_{Pbo}(1)] - [QTc_{Pbo}(-1) - QTc_{Pbo}(14)]$
- ΔΔ: average of the above two.

Example 3: Parallel study with nested xo

- Parallel part



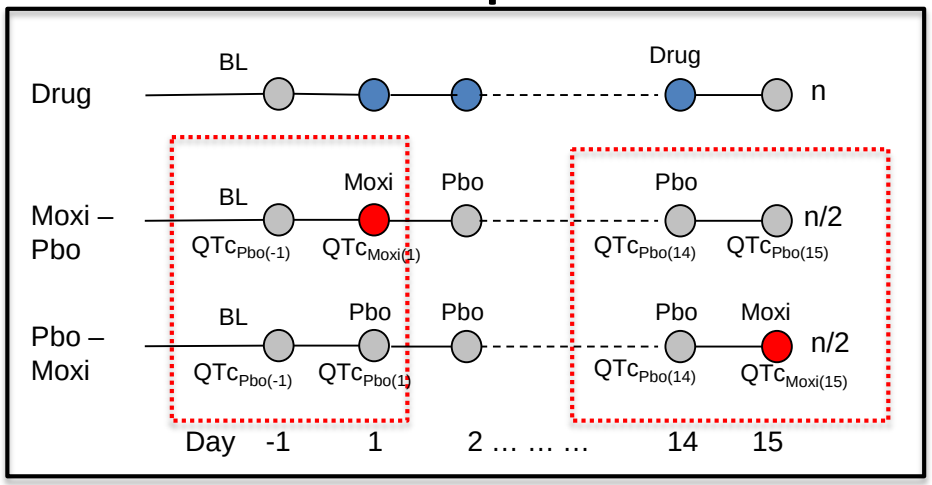


Sequence	Period 1	
	Day -1	Day 14
Supra	Supra ABLFL	**Supra** ANL01FL
Placebo*	Placebo ABLFL, ACOMPFL	**Placebo** ANL01FL,ACOMPFL

* For the parallel part, both the moxi-placebo and placebo-moxi are pooled and called Placebo

Example 3: Parallel study with nested xo

- Crossover part



Nested crossover part

ΔΔ for moxifloxacin (moxi)

- Moxi-Pbo: $[QTc_{Moxi}(1) – QTc_{Pbo}(15)] - [QTc_{Pbo}(14) – QTc_{Pbo}(-1)]$
- Pbo-Moxi: $[QTc_{Moxi}(15) – QTc_{Pbo}(1)] - [QTc_{Pbo}(-1) – QTc_{Pbo}(14)]$
- ΔΔ: average of the above two.

Sequence	Period 1			
	Day -1	Day 1	Day 14	Day 15
Moxi-Pbo	Pbo_{-1}	$Moxi_{1}$	Pbo_{14}	Pbo_{15}
Pbo-Moxi	Pbo_{-1}	Pbo_{1}	Pbo_{14}	$Moxi_{15}$

Nested crossover

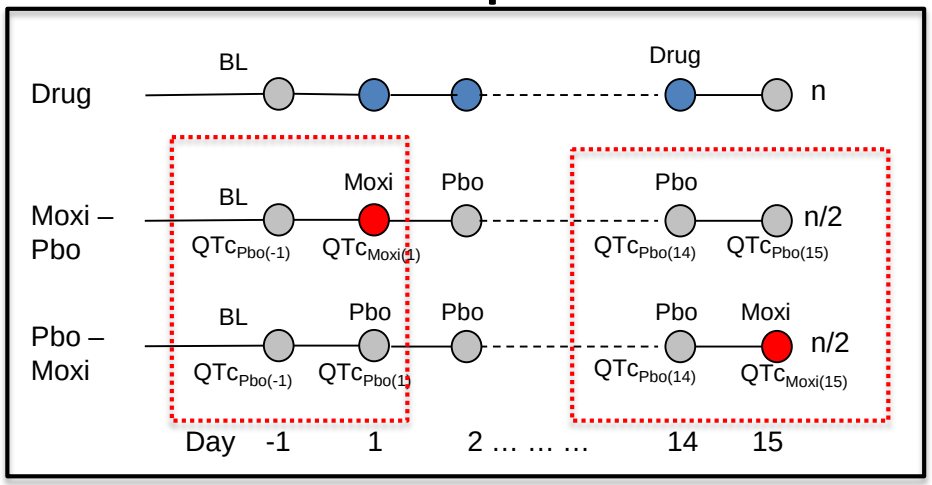
Sequence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
Moxi-Pbo				
Pbo-Moxi				

* For the crossover part, the sequence and treatments are coded like a xo study

** Pbo: Placebo

Example 3: Parallel study with nested xo

- Crossover part



Sequence	Period 1			
	Day -1	Day 1	Day 14	Day 15
Moxi-Pbo	Pbo_{-1}	$Moxi_{1}$	Pbo_{14}	Pbo_{15}
Pbo-Moxi	Pbo_{-1}	Pbo_{1}	Pbo_{14}	$Moxi_{15}$

Nested crossover part

ΔΔ for moxifloxacin (moxi) Day 1 Day -1 (BL)

- Moxi - Pbo: $[QTc_{Moxi}(1) - QTc_{Pbo}(15)]$ - Period 1
  $[QTc_{Pbo}(14) - QTc_{Pbo}(-1)]$ Period 2
- Pbo - Moxi: $[QTc_{Moxi}(15) - QTc_{Pbo}(1)]$ - Period 2
  $[QTc_{Pbo}(-1) - QTc_{Pbo}(14)]$ Period 1
- ΔΔ: average of the above two.

Nested crossover

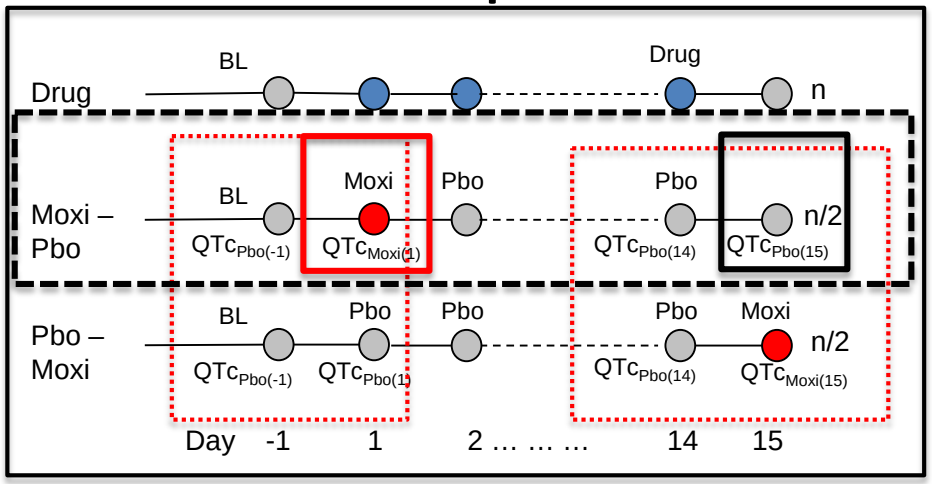
Sequence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
Moxi-Pbo				
Pbo-Moxi				

* For the crossover part, the sequence and treatments are coded like a xo study

** Pbo: Placebo

Example 3: Parallel study with nested xo

- Crossover part: Moxi-Pbo, Period 1



quence	Period 1			
	Day -1	Day 1	Day 14	Day 15
oxi-Pbo	Pbo_{-1}	**$Moxi_1$**	Pbo_{14}	**Pbo_{15}**
o-Moxi	Pbo_{-1}	Pbo_1	Pbo_{14}	$Moxi_{15}$

Nested crossover part

ΔΔ for moxifloxacin (moxi) Day 1 Day -1 (BL)

- Moxi - Pbo: $[QTc_{Moxi}(1) - QTc_{Pbo}(15)]$ - Period 1
  $[QTc_{Pbo}(14) - QTc_{Pbo}(-1)]$ Period 2
- Pbo - Moxi: $[QTc_{Moxi}(15) - QTc_{Pbo}(1)]$ - Period 2
  $[QTc_{Pbo}(-1) - QTc_{Pbo}(14)]$ Period 1
- ΔΔ: average of the above two.

Nested crossover

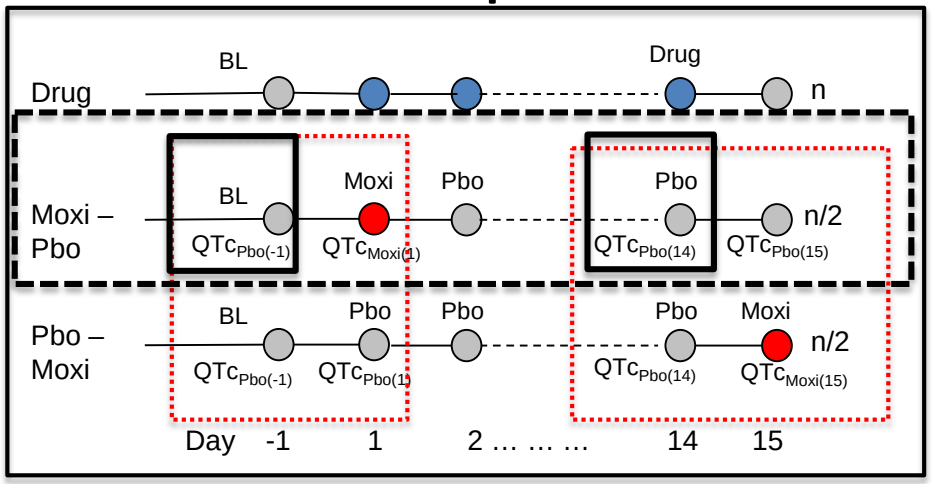
quence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
oxi-Pbo	**Pbo_{15}**	**$Moxi_1$**		
bo-Moxi				

* For the crossover part, the sequence and treatments are coded like a xo study

** Pbo: Placebo

Example 3: Parallel study with nested xo

- Crossover part: Moxi-Pbo, Period 2



quence	Period 1			
	Day -1	Day 1	Day 14	Day 15
oxi-Pbo	**Pbo_{-1}**	$Moxi_1$	**Pbo_{14}**	Pbo_{15}
o-Moxi	Pbo_{-1}	Pbo_1	Pbo_{14}	$Moxi_{15}$

Nested crossover part

ΔΔ for moxifloxacin (moxi) Day 1 Day -1 (BL)

- Moxi - Pbo: $[QTc_{Moxi}(1) - QTc_{Pbo}(15)]$ - Period 1
  $[QTc_{Pbo}(14) - QTc_{Pbo}(-1)]$ Period 2
- Pbo - Moxi: $[QTc_{Moxi}(15) - QTc_{Pbo}(1)]$ - Period 2
  $[QTc_{Pbo}(-1) - QTc_{Pbo}(14)]$ Period 1
- ΔΔ: average of the above two.

Nested crossover

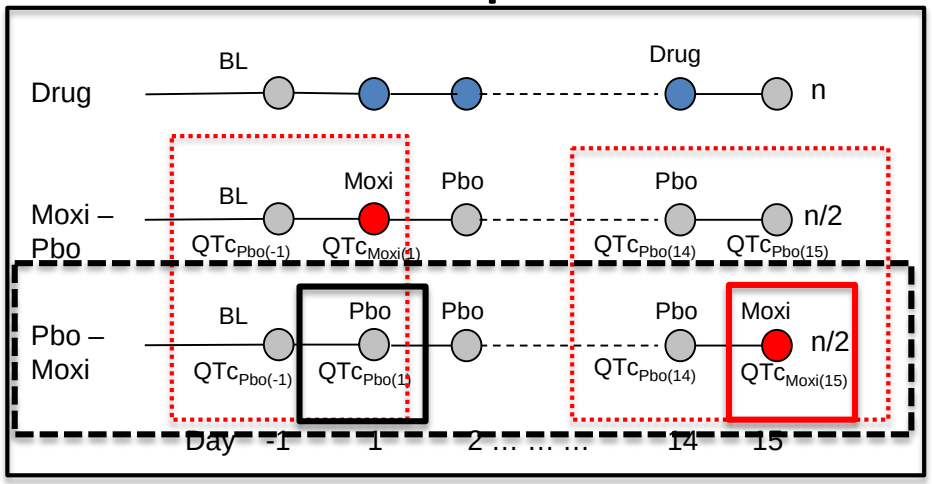
quence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
oxi-Pbo	Pbo_{15}	Mox	**Pbo_{-1}**	**Pbo_{14}**
o-Moxi				

* For the crossover part, the sequence and treatments are coded like a xo study

** Pbo: Placebo

Example 3: Parallel study with nested xo

- Crossover part: Pbo-Moxi, Period 2



Sequence	Period 1			
	Day -1	Day 1	Day 14	Day 15
Moxi-Pbo	**Pbo_{-1}**	$Moxi_1$	**Pbo_{14}**	Pbo_{15}
Pbo-Moxi	Pbo_{-1}	Pbo_1	Pbo_{14}	$Moxi_{15}$

Nested crossover part

ΔΔ for moxifloxacin (moxi) Day 1 Day -1 (BL)

- Moxi - Pbo: $[QTc_{Moxi}(1) - QTc_{Pbo}(15)]$ - Period 1
  $[QTc_{Pbo}(14) - QTc_{Pbo}(-1)]$ Period 2
- Pbo - Moxi: $[QTc_{Moxi}(15) - QTc_{Pbo}(1)]$ - Period 2
  $[QTc_{Pbo}(-1) - QTc_{Pbo}(14)]$ Period 1
- ΔΔ: average of the above two.

Nested crossover

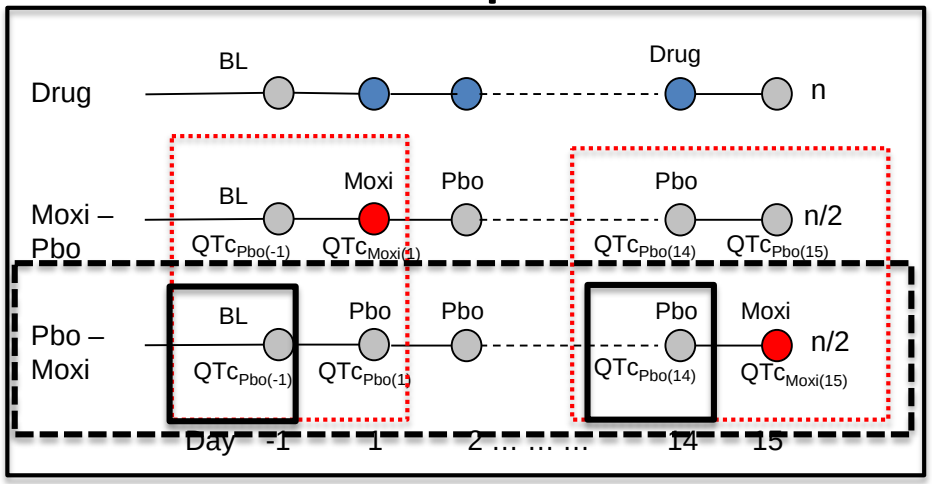
Sequence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
Moxi-Pbo	Pbo_{15}	$Moxi_1$	Pbo_{-1}	Pbo_{14}
Pbo-Moxi			**Pbo_1**	**$Moxi_{15}$**

* For the crossover part, the sequence and treatments are coded like a xo study

** Pbo: Placebo

Example 3: Parallel study with nested xo

- Crossover part: Pbo-Moxi, Period 1



equence	Period 1			
	Day -1	Day 1	Day 14	Day 15
Moxi-Pbo	**Pbo$_{-1}$**	Moxi$_1$	**Pbo$_{14}$**	Pbo$_{15}$
bo-Moxi	Pbo$_{-1}$	Pbo$_1$	Pbo$_{14}$	Moxi$_{15}$

Nested crossover part

ΔΔ for moxifloxacin (moxi) Day 1 Day -1 (BL)

- Moxi - Pbo: [QTc$_{Moxi}$(1) – QTc$_{Pbo}$(15)] - Period 1
  [QTc$_{Pbo}$(14) – QTc$_{Pbo}$(-1)] Period 2
- Pbo - Moxi: [QTc$_{Moxi}$(15) – QTc$_{Pbo}$(1)] - Period 2
  [QTc$_{Pbo}$(-1) – QTc$_{Pbo}$(14)] Period 1
- ΔΔ: average of the above two.

Nested crossover

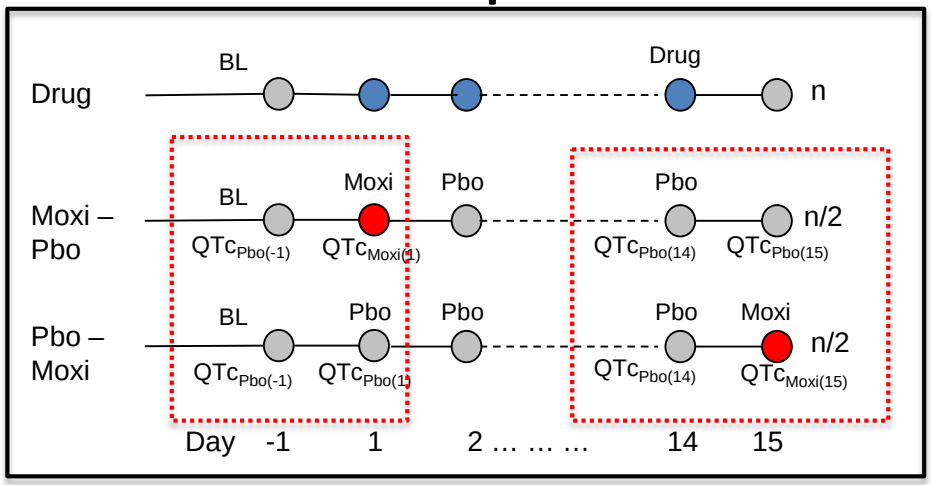
equence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
Moxi-Pbo	Pbo$_{15}$	Moxi$_1$	Pbo$_{-1}$	Pbo$_{14}$
Pbo-Mox	**Pbo$_{14}$**	**Pbo$_{-1}$**	bo$_1$	Moxi$_{15}$

* For the crossover part, the sequence and treatments are coded like a xo study

** Pbo: Placebo

Example 3: Parallel study with nested xo

- Crossover part



Sequence	Period 1			
	Day -1	Day 1	Day 14	Day 15
Moxi-Pbo	Pbo_{-1}	$Moxi_{1}$	Pbo_{14}	Pbo_{15}
Pbo-Moxi	Pbo_{-1}	Pbo_{1}	Pbo_{14}	$Moxi_{15}$

Nested crossover part

ΔΔ for moxifloxacin (moxi)

- Moxi - Pbo: $[QTc_{Moxi}(1) - QTc_{Pbo}(15)] - [QTc_{Pbo}(14) - QTc_{Pbo}(-1)]$
- Pbo - Moxi: $[QTc_{Moxi}(15) - QTc_{Pbo}(1)] - [QTc_{Pbo}(-1) - QTc_{Pbo}(14)]$
- ΔΔ: average of the above two.

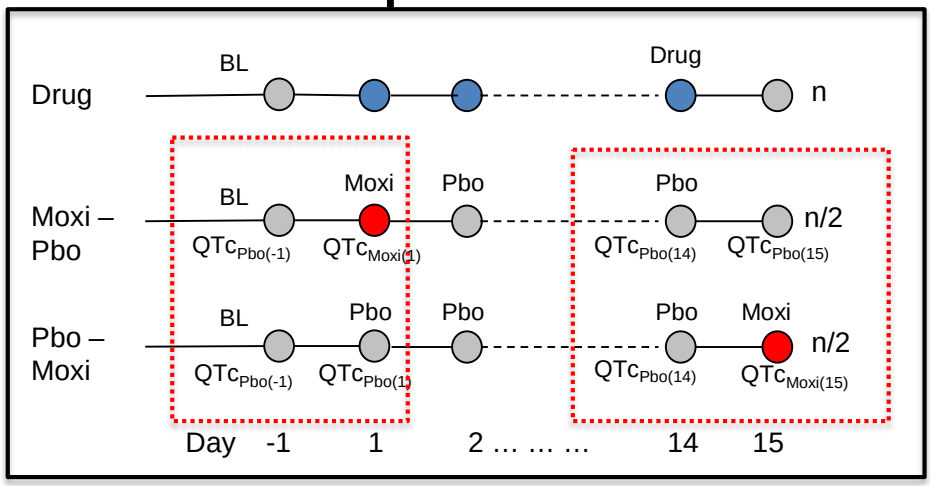
Nested crossover

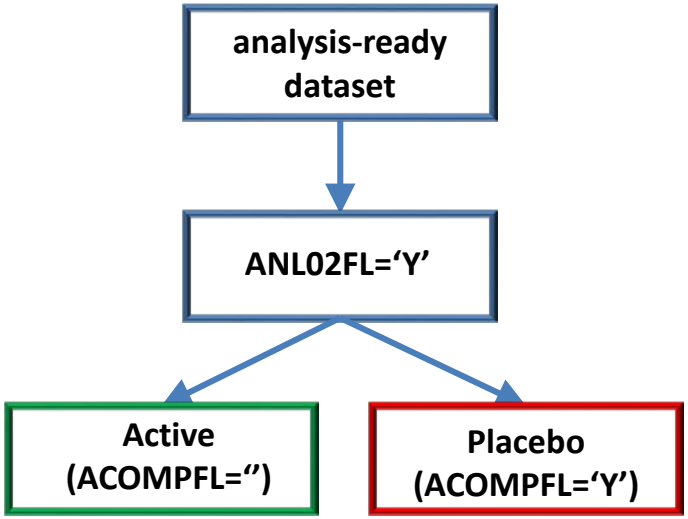
Sequence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
Moxi-Pbo	**Pbo_{15}**	**$Moxi_{1}$**	**Pbo_{-1}**	**Pbo_{14}**
Pbo-Moxi	**Pbo_{14}**	**Pbo_{-1}**	**Pbo_{1}**	**$Moxi_{15}$**

* For the crossover part, the sequence and treatments are coded like a xo study

Example 3: Parallel study with nested xo

- Crossover part





Sequence	Period 1		Period 2	
	Day -1	Day 1	Day -1	Day 1
Moxi-P	Placebo ABLFL	**Moxi** ANL02FL	**Placebo** ANL02FL, ACOMPFL	Moxi ABLFL
Pbo-M	**Placebo** ANL02FL, ACOMPFL	Moxi ABLFL	Placebo ABLFL	**Moxi** ANL02FL

* For the crossover part, the sequence and treatments are coded like a xo study

Additional flags

- Three additional flags used together with ANLxxFL and ACOMPFL allow for encoding the analysis type for each analysis dataset:
  - **IUTANLFL**: rows with IUTANLFL='Y' are to be included in intersection union test (IUT) or central tendency (i.e., by-time) analysis.
  - **CQTANLFL**: rows with CQTANLFL='Y' are to be included in concentration-response analysis (e.g., C-QT).
  - **CATANLFL**: rows with CATANLFL='Y' are included in categorical or outlier analysis.

Examples summary

- No matter the study design, primary analysis for CQT/IUT can be done by filtering by ANL01FL='Y'
- For studies where a different analysis subset is needed for assay sensitivity (e.g., parallel with nested crossover), the rows for assay sensitivity can be extracted by filtering by ANL02FL='Y'
- IUTANLFL, CQTANLFL, and CATANLFL allow for encoding the type of analysis to be performed

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- Lars Johannesen
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- Christine Garnett

Summary

- The Technical Specifications Document for QT studies describes an explicit data format that facilitates analysis of QT study data in an efficient way, by allowing for producing an analysis-ready dataset using a fixed algorithm
- It addresses challenges associated with the increased heterogeneity of study designs used for assessing QT in drug-safety studies that could not be addressed efficiently with existing data standards
- Coding datasets following the Technical Specifications Document is easy because it builds on top of existing data standards (SDTM, ADaM, TAUG-QT) and provides clarity on structure and terminology

Online resources

- Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT)

  https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt

- Technical Specifications Document for QT Studies

  https://www.fda.gov/media/128187/download

- FDA Data Standards Resources

  https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

- Therapeutic Area User Guide for QT studies

  https://www.cdisc.org/sites/default/files/members/standard/ta/qt-studies/taug-qtv10.pdf

- ICH E14

  https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf

- ICH E14 Q&A R3

  https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf