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

Guidance for Industry Technical Specifications Document

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Table of Contents

1.0	Introduction.....	4
2.0	Overview of the Dataset Specifications.....	6
3.0	Dataset Specifications for Analysis Dataset for Electrocardiogram Tests – ADEG	7
3.1	Examples	13
4.0	Dataset Specifications for Pharmacokinetic Concentrations Analysis Dataset – ADPC .	17
4.1	Examples	19
5.0	Appendix: Coding Datasets From Parallel With Nested Crossover Study Design	20

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LIST OF TABLES

Table 1: Analysis Variable Metadata for ADEG.....	8
Table 2: Reduced ADEG Example Illustrating Time Encoding.....	13
Table 3: Reduced AEDG Example Illustrating Multiple Predose Time Points Used for Baseline	14
Table 4: Reduced ADEG Illustrating Use of Basetype in a Subset of Data From a Study With Full Time-Matched Baseline Day.....	15
Table 5: Reduced ADEG Illustrating Use of Comptype in a Subset of Data From a Parallel Study.....	16
Table 6: Analysis Variable Metadata for ADPC.....	17
Table 7: ADEG Example.....	19
Table 8: ADPC Example.....	19
Table 9: Summary of Flags Per Part and Treatment Arm in ADEG for a Parallel Study With Nested Crossover Design.....	22

LIST OF FIGURES

Figure 1: Example of Parallel Study With Nested Crossover Design 20

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1.0 Introduction

This document provides detailed information and specifications for the content of datasets that should be submitted as part of the sponsor's/applicant's application for drugs required to be assessed in clinical studies for their QT/QTc interval prolongation and proarrhythmic potential. These specifications also provide an opportunity for dialogue between the sponsor/applicant and reviewers to discuss issues with trial design or conduct that may affect the content of the analysis datasets. These specifications were built to support the recommendations provided in the International Council for Harmonisation (ICH) guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (ICH E14) and *Therapeutic Area Data Standards User Guide for QT Studies*² (TAUG-QT), and to support the data standards and processes described in the *FDA Study Data Technical Conformance Guide*.³

For questions regarding a specific submission, the sponsor/applicant should contact the applicable review division. For questions about a particular data standard implementation issue, contact cdcr-edata@fda.hhs.gov. For more general recommendations on the use and submission of standardized study data, refer to the *Study Data Technical Conformance Guide*.

¹ This technical specifications document has been prepared by the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2018-D-1216 (available at <https://www.regulations.gov/docket?D=FDA-2018-D-1216>) (see the instructions for submitting comments in the docket).

² <https://www.cdisc.org/sites/default/files/members/standard/ta/qt-studies/taug-qt10.pdf>.

³ <https://www.fda.gov/media/88173/download>.

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

This document provides detailed data specifications for the following datasets:

- **Analysis Dataset for Electrocardiogram Tests (ADEG).** This is a one record per subject per parameter per time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative measures in the electrocardiogram (ECG) and ECG interpretation statements. This ADEG dataset is based on the Analysis Data Model (ADaM) Basic Data Structure (BDS) and designed to comply with the ADEG dataset described in the TAUG-QT. Additional variables and specific derivations from the standard TAUG-QT ADaM-compliant ADEG dataset are described in Table 1. The intent of the additional variables and specific derivations is to aid in FDA's review process.
- **Pharmacokinetic Concentrations Analysis Dataset (ADPC).** This is a one record per subject per pharmacokinetic (PK) parameter per time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative PK measures. This dataset is designed to be a subset of an ADaM-compliant ADPC dataset that allows for concentration-ECG changes analysis (e.g., concentration-QT). Thus, while not all PK samples may have time-matched ECG data, the variables present in both ADEG and ADPC should be coded consistently to allow for proper mapping of time-matched PK and ECG rows. Although this is a subset of ADPC, it also includes additional variables and specific derivations. The additional variables and specific derivations from the standard ADaM-compliant ADPC dataset are described in Table 6. The intent of the additional variables and specific derivations is to aid in FDA's review process.
- **Subject Level Analysis Dataset (ADSL).** This is a one record per subject dataset that contains variables such as subject-level population flags, planned and actual treatments for each period, demographic information, stratification and subgrouping variables, important dates, and so forth. This dataset should be an ADaM-compliant ADSL as described in the *ADaM Implementation Guide* (ADaM IG)⁴ and discussed in the *Study Data Technical Conformance Guide*.

⁴ https://www.cdisc.org/system/files/members/standard/foundational/adam/ADaMIG_v1.1.pdf.

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These three datasets should be accompanied by informative metadata in the form of a compliant Define.xml document that describes the source and derivation of the variables.

2.0 Overview of the Dataset Specifications

Each section below provides a specification that describes the desired content of the dataset. The variable names and associated metadata are based on current Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM)⁵ and ADaM⁶ standards where possible. Each specification includes a column that contains information about the variables, such as the expected content, derivation considerations, or assumptions. If any variable is unclear, sponsors/applicants are encouraged to discuss expectations with FDA's QT Interdisciplinary Review Team (IRT) via the applicable review division.

Some variables may not be appropriate for all clinical trials. If a sponsor's/applicant's trial did not collect the data necessary to create a specified variable, then it is acceptable to omit the variable in the datasets. Variables that have been omitted or added should be documented in the Define.xml file and itemized in the Analysis Data Reviewer Guide (ADRG) as a separate table. Sponsors/applicants should also submit programs that were used to create these datasets (see the *Study Data Technical Conformance Guide*).

Consistency in controlled terminology across SDTM and ADaM as well as across ADaM datasets is important to facilitate traceability and support analyses. Using standard controlled terminology (CT) is preferred where applicable (e.g., Medical Dictionary for Regulatory Activities (MedDRA), CDISC-controlled terminology). For variables without standard CT, where appropriate and to the degree possible, sponsor-/applicant-defined controlled terminology should also be consistent across SDTM and ADaM datasets.

Sometimes the ability to efficiently analyze or trace data depends on the use of consistent CT across datasets. For this reason, the specifications identify explicitly certain parameters and variables where consistent controlled terminology across datasets is expected. For example, to support analyses, the sponsor-/applicant-defined controlled terminology for variables such as AVISIT, ATPT, TRTN, and others should be consistent across ADEG and ADPC or, to support traceability between SDTM and ADaM, the value of PARAM in ADEG should be equivalent to the value of the corresponding EGTEST for parameters that are not derived. In all cases, the variable labels and the variable type noted in the specifications should be used.

⁵ <https://www.cdisc.org/standards/foundational/sdtm>.

⁶ <https://www.cdisc.org/standards/foundational/adam>.

3.0 Dataset Specifications for Analysis Dataset for Electrocardiogram Tests – ADEG

This dataset is a one record per subject per parameter per analysis period per analysis visit per analysis time point dataset that contains a comprehensive set of variables pertaining to the subject and those variables quantitative measures in the ECG and ECG interpretations. Ideally, all of these variables should be traceable to the submitted tabulations or analysis datasets. Whereas the formation of this dataset duplicates information found in other submitted datasets, the compilation of these variable concepts into one record facilitates FDA's statistical and medical reviews.

If the ADEG dataset includes heart rate corrected QT (QTc) values obtained with a formula and coefficients derived by the sponsor/applicant or vendor (i.e., QTc values not created from commonly used historical heart rate correction models such as Fridericia's QT correction), the sponsor/applicant should include the heart rate correction-related information in an Analysis Dataset for ECG QTc Model Data (ADQT) as specified in the TAUG-QT. Such ADQT datasets should also be documented in the Define.xml file.

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Table 1: Analysis Variable Metadata for ADEG

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
STUDYID	Study Identifier	Char		
USUBJID	Unique Subject Identifier	Char		
TRTSEQP	Planned Sequence of Treatments	Char		
TRTP	Planned Treatment	Char		
TRTPN	Planned Treatment (N)	Num		The numeric code for TRTP. One-to-one mapping within ADEG to TRTP. The mapping should be the same in ADEG and ADPC.
TRTSEQA	Actual Sequence of Treatments	Char		
TRTA	Actual Treatment	Char		
TRTAN	Actual Treatment (N)	Num		The numeric code for TRTA. One-to-one mapping within ADEG to TRTA. The mapping should be the same in ADEG and ADPC.
PARAM	Parameter	Char	EGTEST	For records with a corresponding record in ECG test results (EG) dataset (e.g., for QTcF, “QTcF Interval”).
PARAMCD	Parameter Code	Char		Parameter code with a maximum length of 4 characters. One-to-one correspondence with PARAM. For records with a corresponding record in EG, PARAMCD should be EG.EGTESTCD abbreviated up to 4 characters long.
APERIOD	Period	Num		Populate based on EG.VISITNUM. Note there can be 1 or more visits per period. ADEG.APERIOD and ADPC.APERIOD should be coded consistently so mapping of time-matched measures can be performed.
APERIODC	Period (C)	Char		Character version of APERIOD. One-to-one correspondence with APERIOD.
AVISIT	Analysis Visit	Char		Populate based on EG.VISIT.
AVISITN	Analysis Visit (N)	Num		Numeric version of AVISIT. Since study visits are usually defined by certain time points, defining AVISITN so that it represents the time point associated with the visit can facilitate plotting and interpretation of the values. Alternatively, AVISITN may be a protocol visit number, a cycle number, an analysis visit number, or any other number logically related to AVISIT or useful for sorting that is needed for analysis (see ADaM IG).
ATPT	Analysis Time Point	Char		Populate based on EG.EGTPT. EG.EGTPT and PC.PCTPT should be coded in ADEG.ATPT and ADPC.ATPT in a consistent fashion.

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Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
ATPTN	Analysis Time Point (N)	Num		ATPTN provides a numeric representation of ATPT. Defining ATPTN so that its values represent the planned time points in a consistent unit (e.g., minutes or hours after dosing) is not required but can facilitate plotting and interpretation of the values. Within the same parameter, there is a one-to-one mapping between ATPT and ATPTN (see ADaM IG). As for ATPT, the coding of ATPTN should be the same for ADEG.ATPTN and ADPC.ATPTN.
ATPTREF	Analysis Reference Time Point	Char		Populate based on EG.EGTPREF. Description of the fixed reference point referred to by ATPT/ATPTN (e.g., time of dose). For example, "Morning Dose" could be the reference point used. As for ATPT, the coding of ATPTREF should be the same for ADEG and ADPC.
ARDTM	Date/Time of Reference	Num		Date and time of reference. ARDTM provides a date and time representation of ATPTREF. As for ATPTREF, ARDTM should be the same for ADEG and ADPC. Please see Table 2 below as well as the Appendix for examples.
AARDTM	Actual Date/Time of Reference	Num		Actual date and time of reference of ARDTM.
ARRLT	Actual Relative Time from Reference TPT	Num		This is the actual elapsed time (for sample point or start of sampling interval) from reference date and time (ADTM - ARDTM).
NRRLT	Nominal Relative Time from Ref TPT	Num		This is the planned elapsed time (for sample point or start of sampling interval) from reference date and time (ARDTM).
RRLTU	Relative Time from Reference TPT Units	Char	UNIT	Units for all elapsed time variables (i.e., *RRLT) from reference time point (ATPTREF).
ADTM	Analysis Date and Time	Num		Populate from EG.EGDTC.
ADT	Analysis Date	Num		Numeric date value from EG.EGDTC.
ATM	Analysis Time	Num		Numeric time value from EG.EGDTC.
ADY	Analysis Relative Day	Num		Populate based on EG.EGDY.
AVISDY	Analysis Visit Day	Num		
APERDAY	Analysis Nominal Period Day	Num		Populate with the numeric relative day within the Period based on AVISITN. For example, "Period 2 Day 1" is APERDAY=1. ADEG.APERDAY and ADPC.APERDAY should be coded consistently so mapping of time-matched measures can be performed.
EGREPNUM	ECG Replicate Number	Num		Populate with EG.REPNUM for non-derived records. Number of ECG replicates within time point.

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Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
AVAL	Analysis Value	Num		Populate with EG.EGSTRESN for non-derived records. Also create derived records for the average of the individual replicate values for ECG measurements collected at each nominal time point (e.g., average of triplicates).
AVALC	Analysis Value (C)	Char		Populate with EG.EGSTRESC.
AVALU	Units of Analysis Value	Char	UNIT	Populate with EG.EGSTRESU.
DTYPE	Derivation Type	Char	DTYPE	Type of derivation (e.g., DTYPE="AVERAGE" for records containing the average of the replicate values for each time point).
ABLFL	Baseline Record Flag	Char	Y	Character indicator to identify the baseline record for each subject, parameter, and baseline type (BASETYPE) combination.
AEGBLFL	Flag for Records used to Derive the Baseline	Char	Y	If record was used to derive the baseline, then AEGBLFL="Y" else AEGBLFL is null.
BASE	Baseline Value	Num		The subject's baseline analysis value for a parameter and baseline definition (i.e. BASETYPE). BASE contains the value of AVAL copied from a record within the parameter on which ABLFL eq "Y" and same BASETYPE. Note that a baseline record may be derived (e.g., it may be an average) in which case DTYPE should be populated on the baseline record.
CHG	Change from Baseline	Num		If ABLFL ne "Y" and DTYPE eq "AVERAGE" then CHG=AVAL – BASE.
BASETYPE	Baseline Type	Char		Encodes the key that allows for identifying baseline rows that correspond to each DTYPE eq "AVERAGE" and ABLFL ne "Y".
ACOMPFL	Comparator Record Flag	Char	Y	If record is part of the comparator treatment (e.g., placebo) then ACOMPFL="Y" else ACOMPFL is null.
COMP	Comparator Value	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMP=AVAL; else COMP value is based on the corresponding COMPTYPE (see BASETYPE).
COMPBASE	Baseline Value of the Comparator	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMPBASE=BASE else COMPBASE value is based on the corresponding COMPTYPE.
COMPCHG	Change from Baseline in the Comparator	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMPCHG=CHG else COMPCHG value is based on the corresponding COMPTYPE.
CCOMPCHG	Comparator corrected change from BL	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL ne "Y" then CCOMPCHG=CHG – COMPCHG else null.
COMPTYPE	Comparator Type	Char		Encodes the key that allows for identifying comparator treatment (e.g., placebo) rows used to compute the comparator and baseline corrected changes (i.e., double deltas) from

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Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
				each DTYPE eq "AVERAGE" and ACOMPFL ne "Y". This is similar to BASETYPE above.
ECGPCFL	ECG Matching PK Flag	Char		Populate with "Y" if there is a matching nominal PK sample time point for the nominal ECG time point (i.e., if there are time-matched PK measures in ADPC for this ECG).
EGSEQ	Sequence Number	Num		Populate with EG.EGSEQ. Missing for derived records.
EGLEAD	Lead Location Used for Measurement	Char	EGLEAD	Populate with EG.EGLEAD.
EGREFID	ECG Reference ID	Char		Populate with EG.EGREFID. Missing for derived records.
CRITY	Analysis Criterion y	Char		A text string identifying a pre-specified criterion within a parameter, for example QTcF \geq 500. Required if CRITYFL exists (see ADaM IG).
CRITYFL	Criterion y Evaluation Result Flag	Char	Y	Character flag variable indicating whether the criterion defined in CRITY was met by the data on record. See CRITY for more information regarding how to use CRITY and CRITYFL to indicate whether a criterion is met (see ADaM IG).
IUTANLFL	Intersection Union Test Analysis Flag	Char	Y	Character flag variable set to "Y" if the record is used in the intersection union test (i.e., by-time) analysis or null otherwise.
CATANLFL	Categorical Analysis Flag	Char	Y	Character flag variable set to "Y" if the record is used in the categorical analysis or null otherwise.
CQTANLFL	Concentration QT Analysis Flag	Char	Y	Character flag variable set to "Y" if the record is used in the concentration-QT analysis or null otherwise.
ANL01	Analysis 01	Char		A text string describing the analysis number 01, which is reserved for the primary analysis (e.g., assessment of investigational drug treatment QT effects).
ANL01FL	Analysis Flag 01	Char	Y	Selection variable to identify the exact set of records used in the analysis number 01 corresponding to ANL01.
ANL02	Analysis 02	Char		A text string describing the analysis flag number 02, which is reserved for the assay sensitivity analysis (e.g., assessment of positive control QT effects).
ANL02FL	Analysis Flag 02	Char	Y	Selection variable to identify the exact set of records used in the analysis number 02 corresponding to ANL02.
ANLzz	Analysis zz	Char		A text string describing the analysis flag number zz. Note that $zz \geq 03$ because ANL01 and ANL02 are reserved for investigational drug and assay sensitivity analyses, respectively.

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Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
ANLzzFL	Analysis Flag zz	Char	Y	Selection variable to identify the exact set of records used in the analysis number zz (e.g., any analysis that was not investigational drug or assay sensitivity). Note that $zz \geq 03$ is because ANL01FL and ANL02FL are reserved for investigational drug and assay sensitivity analyses, respectively.

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3.1 Examples

The examples below are reduced examples and only contain a few time points per period per period day for one or a limited number of subjects and DTYPE eq “AVERAGE” for illustration purposes.

Two reduced examples are provided below for time-matched (Table 2) and pre-dose (Table 3) baseline definitions in order to illustrate the recommended approach to encode time information, ABLFL, and AEGBLFL. ARDTM is a numerical value representing the date and time. To facilitate readability, the value of this variable is displayed as a date and time string.

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

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

USUBJID	TRTA	ABLFL	AEGBLFL	AVAL	APERIOD	APERDAY	ATPT	ATPTN	ATPTREF	ARDTM	NRRLT	RRLTU
1002	Placebo		Y	381.133	1	1	-1 h	1	Morning dose	2018-05-21T08:00:00	-1	Hours
1002	Placebo		Y	380.066	1	1	-0.5 h	2	Morning dose	2018-05-21T08:00:00	-0.5	Hours
1002	Placebo		Y	380.632	1	1	0 h	3	Morning dose	2018-05-21T08:00:00	0	Hours
1002	Placebo	Y		380.610	1	1	Baseline	4	Morning dose	2018-05-21T08:00:00	0	Hours
1002	Placebo			378.179	1	1	0.5 h	5	Morning dose	2018-05-21T08:00:00	0.5	Hours
1002	Placebo			376.497	1	1	1 h	6	Morning dose	2018-05-21T08:00:00	1	Hours
1002	Placebo			366.803	1	1	4 h	7	Morning dose	2018-05-21T08:00:00	4	Hours
1002	Moxi		Y	395.322	2	1	-1 h	1	Morning dose	2018-05-28T08:00:00	-1	Hours
1002	Moxi		Y	393.478	2	1	-0.5 h	2	Morning dose	2018-05-28T08:00:00	-0.5	Hours
1002	Moxi		Y	392.465	2	1	0 h	3	Morning dose	2018-05-28T08:00:00	0	Hours
1002	Moxi	Y		393.755	2	1	Baseline	4	Morning dose	2018-05-28T08:00:00	0	Hours
1002	Moxi			400.421	2	1	0.5 h	5	Morning dose	2018-05-28T08:00:00	0.5	Hours
1002	Moxi			383.874	2	1	1 h	6	Morning dose	2018-05-28T08:00:00	1	Hours
1002	Moxi			378.260	2	1	4 h	7	Morning dose	2018-05-28T08:00:00	4	Hours

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Another reduced example is provided in Table 4 to illustrate the use of BASETYPE. The table only shows rows with DTYPE eq “AVERAGE”, which contain the average value of AVAL of the parameters measured in the individual ECG waveforms grouped by USUBJID, APERIOD, APERDAY, NRRLT, and PARAMCD. In this example, the study had a full time-matched baseline day (Day -1). Thus, BASETYPE has the time-matched key for each subject and time point. AVAL values from the rows with ABLFL eq “Y” get propagated (arrows) to the BASE column of the rows with the same BASETYPE for each subject. BASE is then used to compute the change from baseline of each row as $CHG = AVAL - BASE$. For example, subject 1002 had a QTcF of 375.000 msec at NRRLT 1h at baseline (i.e., 1 hour after DAY -1 Morning dose). Therefore, the change from baseline on Day 14 at NRRLT 1h in this example is $CHG = AVAL - BASE = 375.667 - 375.000 = 0.667$ msec.

Table 4: Reduced ADEG Illustrating Use of BASETYPE in a Subset of Data From a Study With Full Time-Matched Baseline Day

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

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Lastly, Table 5 illustrates the use of COMPTYPE in a parallel study from one subject from the active treatment arm (ACOMPFL eq “”) and the 6 subjects from the placebo arm (ACOMPFL eq “Y”). Table 5 shows QTcF data from DTYPE eq “AVERAGE” rows. The cells with thicker borders highlight the COMPTYPE matched rows. The COMP values are computed as the average of AVAL values of placebo data (ACOMPFL eq “Y”) grouped by COMPTYPE. COMPBASE and COMPCHG values are computed in a similar fashion using the values from BASE and CHG columns, respectively. Finally, the comparator change from baseline (i.e., double delta) is computed as CCOMPCHG = CHG – COMPCHG. Note that for crossover designs, where each subject is his or her own control, USUBJID should be included in COMPTYPE. For example, COMPTYPE = “1001, placebo at 0.5 h” for USUBJID eq “1001”.

Table 5: Reduced ADEG Illustrating Use of COMPTYPE in a Subset of Data From a Parallel Study

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	-5.000		390.111	393.389	-3.278	-1.722	Placebo group at 1 h
1001	Drug	4	387.333	381.000	6.333	average	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

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4.0 Dataset Specifications for Pharmacokinetic Concentrations Analysis Dataset – ADPC

This is a one record per subject per PK parameter per analysis period per analysis visit per analysis time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative pharmacokinetic measures. This dataset is designed to be a subset of an ADaM-compliant ADPC dataset that allows for concentration-ECG changes analysis (e.g., concentration-QT). Thus, while not all PK samples may have time-matched ECG data, the variables present in both ADEG and ADPC should be coded consistently to allow for proper mapping of time-matched PK and ECG rows. Ideally, these variables should be traceable to the submitted tabulations and/or analysis datasets. Whereas the formation of this dataset duplicates information found in other submitted datasets, the compilation of these variable concepts into one record facilitates FDA’s statistical and medical reviews.

Table 6: Analysis Variable Metadata for ADPC

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
STUDYID	Study Identifier	Char		
USUBJID	Unique Subject Identifier	Char		
TRTSEQP	Planned Sequence of Treatments	Char		
TRTP	Planned Treatment	Char		
TRTPN	Planned Treatment (N)	Num		The numeric code for TRTP. One-to-one mapping within ADEG to TRTP. The mapping should be the same in ADEG and ADPC.
TRTSEQA	Actual Sequence of Treatments	Char		
TRTA	Actual Treatment	Char		
TRTAN	Actual Treatment (N)	Num		The numeric code for TRTA. One-to-one mapping within ADEG to TRTA. The mapping should be the same in ADEG and ADPC.
APERIOD	Period	Char		Populate based on PC.VISITNUM. Note there can be 1 or more visits per period. ADEG.APERIOD and ADPC.APERIOD should be coded consistently so mapping of time-matched measures can be performed.
APERIODC	Period (C)	Num		Character version of APERIOD. One-to-one correspondence with APERIOD.
AVISIT	Analysis Visit	Char		Populate based on PC.VISIT.
AVISITN	Analysis Visit (N)	Num		Numeric version of AVISIT. Since study visits are usually defined by certain time points, defining AVISITN so that it represents the time point associated with the visit can facilitate plotting and interpretation of the values. Alternatively, AVISITN may be a protocol visit number, a cycle number, an analysis visit number, or any other number logically related to AVISIT or useful for sorting that is needed for analysis (see ADaM IG).

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Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
ATPT	Analysis Time Point	Char		Populate based on PC.PCTPT. EG.EGTPT and PC.PCTPT should be coded in ADEG.ATPT and ADPC.ATPT in a consistent fashion so mapping of time-matched measures can be performed.
ATPTN	Analysis Time Point (N)	Num		ATPTN provides a numeric representation of ATPT. Defining ATPTN so that its values represent the planned time points in a consistent unit (e.g., minutes or hours after dosing) is not required but can facilitate plotting and interpretation of the values. There should be a one-to-one mapping between ATPT and ATPTN (see ADaM IG). As for ATPT, the coding of ATPTN should be the same for ADEG.ATPTN and ADPC.ATPTN.
ATPTREF	Analysis Reference Time Point	Char		Populate based on PC.PCTPTREF. Description of the fixed reference point referred to by ATPT/ATPTN (e.g., time of dose). As for ATPT, the coding of ATPTREF should be the same for ADEG and ADPC.
ARDTM	Date/Time of Reference	Num		Date and time of reference. ARDTM provides a date and time representation of ATPTREF. As for ATPTREF, ARDTM should be the same for ADEG and ADPC.
AARDTM	Actual Date/Time of Reference	Num		Actual date and time of reference of ARDTM.
ARRLT	Actual Relative Time from Reference TPT	Num		This is the actual elapsed time (for sample point or start of sampling interval) from reference date and time (ADTM - ARDTM).
NRRLT	Nominal Relative Time from Reference TPT	Num		This is the planned elapsed time (for sample point or start of sampling interval) from reference date and time (ARDTM).
RRLTU	Relative Time from Reference TPT Units	Char	UNIT	Units for all elapsed time variables (i.e., -RRLT) from reference time point (ATPTREF).
ADTM	Analysis Date and Time	Num		Populate from PC.PCDTC.
ADT	Analysis Date	Num		Numeric date value from PC.PCDTC.
ATM	Analysis Time	Num		Numeric time value from PC.PCDTC.
ADY	Analysis Relative Day	Num		Populated based on PC.PCDY.
AVISDY	Analysis Visit Day	Num		
APERDAY	Analysis Nominal Period Day	Num		Populate with the numeric relative day within the Period based on AVISITN. [For example, "Period 2, Day 1" is APERDAY=1]. ADEG.APERDAY and ADPC.APERDAY should be coded consistently so mapping of time-matched measures can be performed.
PARAM	Analyte Name	Char		Analyte name from PC.PCTEST.
PARAMCD	Parameter Code	Char		Analyte code with a maximum length of 4 characters. Analyte code from PC.PCTESTCD should be abbreviated up to 4 characters long. One-to-one correspondence with PCTEST.
AVAL	Analysis Value	Num		Populate based on PC.PCSTRESN.
AVALU	Units of Analysis Value	Char	PKUNIT	Populate based on PC.PCSTRESU.
LLOQFL	Lower Limit of Quantification Flag	Char	Y	If record value was below the lower limit of quantification, then LLOQFL ="Y" else LLOQFL is null.
PCSEQ	Sequence Number	Num		Populate based on PC.PCSEQ.

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4.1 Examples

A key point in the ADEG and ADPC definitions is that time information for time points with both ECG and PK samples (i.e., ECGPCFL eq “Y”) should be consistent. Additionally, the format allows for time point without both ECG and PK samples collected. A reduced example is presented below to illustrate these points. In Table 7, the row for 12 hours after the morning dose in ADEG has ECG data that has no PK sample data-associated ADPC in Table 8. Similarly, the PK sample collected 14 hours after the morning dose in ADPC has no ECG data associated in ADEG. Please note that this a reduced example for illustration purposes and only contains a few time points per period day for one subject.

Table 7: ADEG Example

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

Table 8: ADPC Example

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

5.0 Appendix: Coding Datasets From Parallel With Nested Crossover Study Design

This appendix contains recommendations about how to code data from a randomized placebo-controlled parallel design QT study with a nested crossover arm for the positive control (Figure 1) in ADEG and ADPC datasets.

Figure 1: Example of Parallel Study With Nested Crossover Design⁷

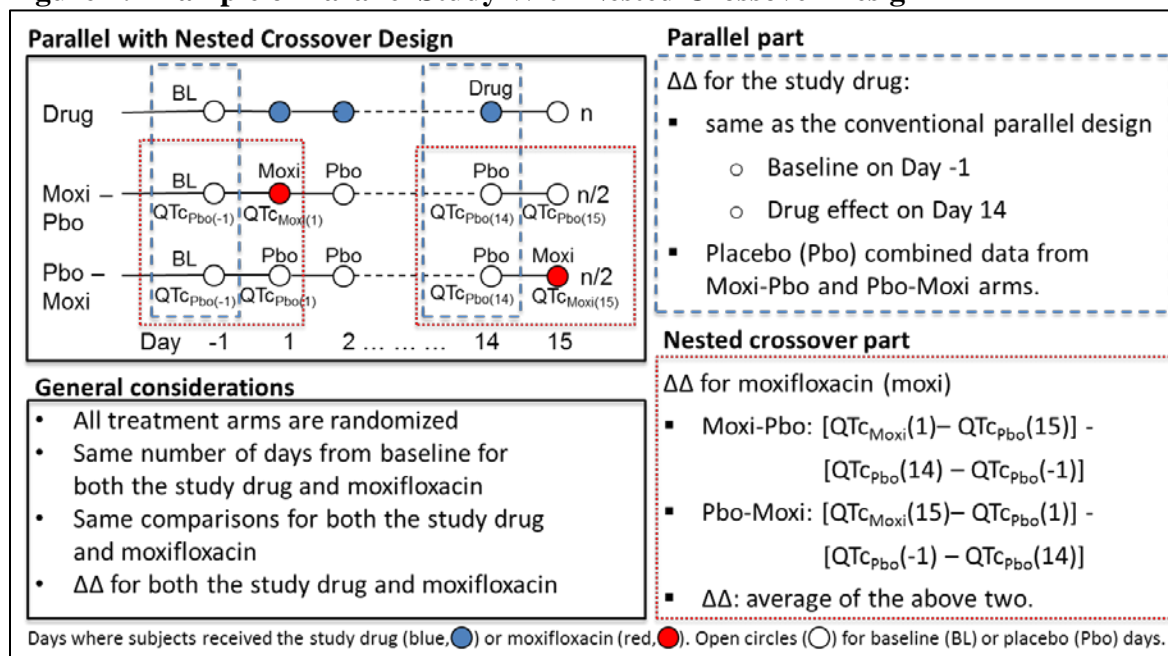


Figure 1 describes a randomized, placebo- (Pbo) controlled, parallel design study with a nested crossover design. Briefly, the two-part study uses time-matched baseline and moxifloxacin (Moxi) as the positive control:

1. A parallel part where the drug and placebo are administered for 14 days and the effect of the drug is evaluated on Day 14 (dashed blue boxes); and
2. A nested crossover part where the Pbo/Moxi treatment group is divided into two arms (Moxi-Pbo, and Pbo-Moxi), with half of the subjects in each (dotted red boxes). In the Moxi-Pbo arm, the positive control (Moxi) is given on Day 1, followed by placebo to Day 15. In the Pbo-Moxi arm, placebo is given on Day 1 to Day 14 and positive control (Moxi) on Day 15.

In the example described in Figure 1, each study part has the same number of subjects. For example, if the parallel part has 40 subjects, then the nested crossover part should include 40

⁷ Adapted from Zhang J, Moxifloxacin Can be Given Within the Placebo Cohort During a Parallel-Designed Thorough QT Study - FDA Perspective. DIA Cardiovascular Safety, QT, and Arrhythmia in Drug Development, Bethesda, Maryland, 2009.

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subjects (20 subjects per arm). This study design therefore provides an example of coding both parallel and crossover studies. Note that this design results in different baseline definitions for each study part (right panels in Figure 1). In Figure 1, all placebo data from Day 14 are used together with baseline data from Day -1 when used in the parallel part and in the Moxi-Pbo arm of the nested crossover part. However, in the Pbo-Moxi arm of the nested crossover part, the data from Day 14 are coded as baseline and the data from Day -1 data are coded as placebo. Note also that, in the Pbo-Moxi arm, the data from Day 1 are coded as baseline in the nested crossover part but not used in the parallel part. Data from a parallel study with a nested crossover design can be coded in one ADEG and one ADPC dataset. The ADPC dataset can be coded following the specifications in the main body of this document. Recommendations for coding the ADEG dataset are provided below.

For the parallel part in the example presented in Figure 1, Day -1 contains the baseline data and drug effects in QT corrected for placebo are assessed on Day 14. Thus, all Day -1 rows will have ABLFL set to “Y” and Day 14 rows will have ANL01FL set to “Y” as well as IUTANLFL and/or CQTANLFL set to “Y”, as appropriate. In addition, rows from Moxi-Pbo and Pbo-Moxi arms on Day 14 will have ACOMPFL set to “Y” because the placebo is the comparator in this example. While subjects in the nested crossover part received moxifloxacin on Day 1 and Day 15, only placebo data will be included in the analysis of the parallel part because only rows from Day 14 have ANL01FL set to “Y”. Note that Day -1 rows have ABLFL set to “Y” but ANL01FL set to null.

For the nested crossover part, only data from the Moxi-Pbo and Pbo-Moxi arms are used. For the Moxi-Pbo arm, the baseline data come from Day 15 and Day -1 for the moxifloxacin day (Day 1) and placebo day (Day 14), respectively (Figure 1). To facilitate analysis, the nested crossover data needs to be coded like a cross-over study with two periods. Thus, Day -1 and Day 15 will have ABLFL set to “Y”, Day 1 and Day 14 will have ANL02FL set to “Y”, and IUTANLFL and/or CQTANLFL will be set to “Y”, as appropriate. Additionally, Days 1 and 14 will be coded as Day 1 and Days -1 and 15 as -1 and period will be set to 1 for the moxifloxacin day (and baseline) and 2 for the placebo day (and baseline). Lastly, Day 14 will have ACOMPFL set to “Y” because this day has the placebo data for this arm. For the Pbo-Moxi arm, the baseline data come from Day 1 and Day 14 for the moxifloxacin day (Day 15) and placebo day (Day -1), respectively. Thus, Day 1 and Day 14 will have ABLFL set to “Y”, Day -1 and Day 15 will have ANL02FL set to “Y”, and IUTANLFL and/or CQTANLFL will be set to “Y”, as appropriate. Similar to the other arm, the Days 15 and -1 will be coded as Day 1 and Days 1 and 14 as Day -1 and the placebo day (and baseline) will be coded as period 1 and moxifloxacin day (and baseline) as period 2. Finally, Day -1 will have ACOMPFL set to “Y” because this day has the placebo data for this arm.

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In both parts, IUTANLFL and CQTANLFL are populated as described above but also take into account whether the analysis of QT effects is to be performed either using by time analysis (IUTANLFL) or using concentration-QT modeling (CQTANLFL), or both.

Table 9: Summary of Flags Per Part and Treatment Arm in ADEG for a Parallel Study With Nested Crossover Design

Part	Arm	Study day			
		Day -1	Day 1	Day 14	Day 15
Parallel	Drug	ABLFL		TRTx = "Drug" IUTANLFL CQTANLFL ANL01FL	
	Moxi-Pbo	ABLFL		TRTx = "Placebo" ACOMPFL IUTANLFL CQTANLFL ANL01FL	
	Pbo-Moxi	ABLFL		TRTx = "Placebo" ACOMPFL IUTANLFL CQTANLFL ANL01FL	
Nested Crossover	Moxi-Pbo	ABLFL ²	TRTx = "Moxi" IUTANLFL CQTANLFL ANL02FL ¹	TRTx = "Placebo" ACOMPFL IUTANLFL CQTANLFL ANL02FL ²	ABLFL ¹
	Pbo-Moxi	TRTx = "Placebo" ACOMPFL IUTANLFL CQTANLFL ANL02FL ²	ABLFL ¹	ABLFL ²	TRTx = "Moxi" IUTANLFL CQTANLFL ANL02FL ¹

¹: Represented in data as Period 1, Day -1 (ABLFL eq "Y") and Day 1 (ABLFL eq ""); ²: Represented in data as Period 2, Day -1 (ABLFL eq "Y") and Day 1 (ABLFL eq "")

Placebo data should be coded consistently in TRTx as "Placebo" when building an ADEG dataset. Table 9 summarizes which flags should be populated with "Y" for each part and treatment arm in the ADEG dataset. Presence of xxFL in a cell in Table 9 indicates that the FL column is set to "Y": otherwise it is not defined. While it may seem that there could be duplicated rows when implementing this approach, the BASETYPE variable will maintain uniqueness of rows from the nested crossover part that have multiple baseline definitions.