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Unlocking the Potential: Exploring Overlooked FDA Guidance for CDISC Implementers

Presented by Angelo Tinazzi, Senior Director
CDISC Europe Coordinating Committee (E3C)

Meet the Speaker

Angelo Tinazzi

Title: Senior Director

Organization: CDISC Europe Coordinating Committee (E3C)

Angelo is a member of the CDISC Europe Coordinating Committee since 2015, where he is also leading the Italian speaking User network.

Angelo has more than 25 years of experience in different biometric organizations. He has a passion for clinical standards as well as programming and he has done several data submissions to both the FDA and the PMDA.

Angelo is also an authorized CDISC instructor for ADaM.

Angelo is Italian, living in France and working in Switzerland.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

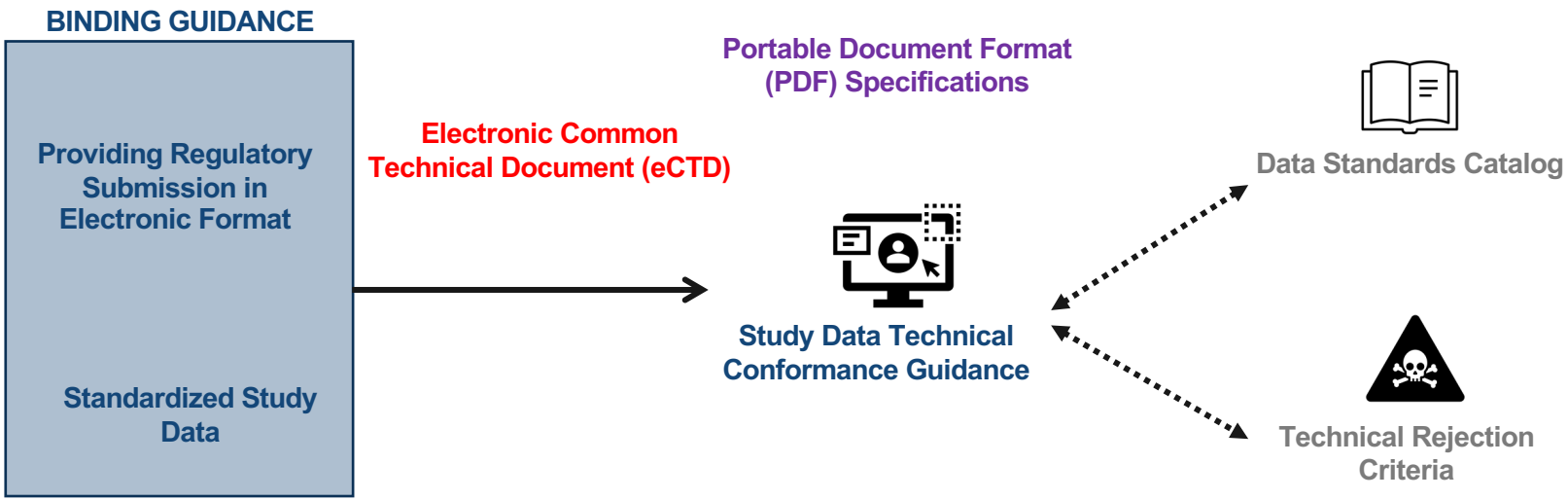
- *I have no real or apparent conflicts of interest to report.*

Agenda

1. FDA Data Submission Technical Guidance
2. Overview of the “Additional” FDA Data Technical Guidance
3. Conclusions

FDA Data Submission Technical Guidance

FDA Data Technical Specifications Guidance



FDA Data Technical Specifications Guidance Other Guidance / Document

- Referenced **CDISC TAUGs** in the FDA SDTCG
- Providing Regulatory Submissions in Electronic Format - General **Considerations, 1999 (Legacy Submission)**
- **Bioresearch Monitoring** Technical Conformance Guide Technical Specifications
- Creating **Simplified TS.XPT** Files
- Submit an eCTD or Standardized Data **Sample** to the FDA (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda)
- Model Data Format for submitting **pharmacometric data and models** (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format)

FDA Data Technical Specifications Guidance

Can you cite any other FDA guidance?

√ Endpoint **Bioequivalence** Study Analysis Datasets for Abbreviated NDA

X Technical Specifications for Submitting Clinical Trial Datasets for **Treatment of Advanced Breast Cancer**

√ Technical Specifications for Submitting Clinical Trial Data Sets for **Treatment of NASH**

X **Diabetes** Technical Specification Guidance

√ **Vaccines** Technical Specification Guidance

√ Submitting Select Clinical Trial Data Sets for **Human Immunodeficiency Virus-1 Infection**

X **ISS and ISE** Datasets Integration for NDA

√ **QT Studies** Technical Specification Document

Can you cite any other FDA guidance?

All these guidance are referenced in the **FDA SDTCG in the section 5 "List of FDA Technical Specification Documents"** and at the **Study Data Standards Resources FDA webpage** in the section **"3. Technical Guidance"** and listed in the table **FDA Study Data Standards Resources**

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

Overview of the “Additional” FDA Data Technical Guidance

Overview of Additional FDA Data Technical Guidance

#	FDA Additional Data Standards Guidance References	SDTM	ADaM	Other
1	**Vaccines** Technical Specification Guidance v2.1 (Apr 2018 / Dec 2019) 10 Pages	√		CRF design recommendations
2	**QT Studies** Technical Specification Document v1.0 (Jun 2019) 24 Pages		√	Good examples
3	Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat **Human Immunodeficiency Virus-1 Infection** v1.0 29 Pages (Mar 2018)		√	Big Summary SL dataset
4	Technical Specifications—**Comparative Clinical Endpoint Bioequivalence Study** Analysis Datasets for Abbreviated New Drug Applications v.1.0 (Sep 2018) 46 Pages		√	
5	Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of **Noncirrhotic Nonalcoholic Steatohepatitis (NASH)** v1.1 44 Pages (Aug 2021 / Jan 2022)	√	√	Controlled Terminology NSV Good examples

Overview of Additional FDA Data Technical Guidance

Vaccines Technical Specification Guidance

CBER Division (OVRR Unit)

SDTM Only

Required domains
IS/MB vs LB
Use of **RELREC** is recommended
Efficacy Data Mapping
CRF design and mapping recommendations for **Reactogenicity** (flat vs nested model)

Ref. Vaccine CDISC TAUG

Overview of Additional FDA Data Technical Guidance
QT Studies Technical Specification Document

CDER Division

ADaM Only

ADEG (examples, use of BASETYPE)

ADPC

Recommend use of **consistent CT** e.g., for AVISIT

Ref. QT CDISC TAUG

Overview of Additional FDA Data Technical Guidance

Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat Human Immunodeficiency Virus-1 Infection

CDER Division

ADaM Only

ADAE (non-OCCDS)

ADLB (list of main laboratory parameters of interest, including Viral Load)

ADEFFOUT (ADSL-like focusing on efficacy endpoints plus many other **"summary" variables**)

Ref. HIV CDISC TAUG

Overview of Additional FDA Data Technical Guidance

Technical Specifications—Comparative Clinical Endpoint Bioequivalence Study Analysis Datasets for Abbreviated NDAs

CDER Division

ADaM Only

ADSL (cross-over study) and other **ADaM specific for each type of study Bioequivalence study**

Definition of mITT population

Suggested PARAMCD/PARAM

Overview of Additional FDA Data Technical Guidance

Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH)

CDER Division, 44 pages

SDTM (14 domains)

- **Events adjudication** recommendations (ZA)
- Correct mapping into **MB for Hepatitis A Virus Antibody**
- Recommend **RELREC** e.g., to link AE and CM

ADaM (7 domains)

- **"Dual" standard unit** reporting SI and US Conv Unit
- Key **time to event** e.g., Time to Liver Transplant
- Several baseline characteristics / "value" (ADSL)
- Good Traceability

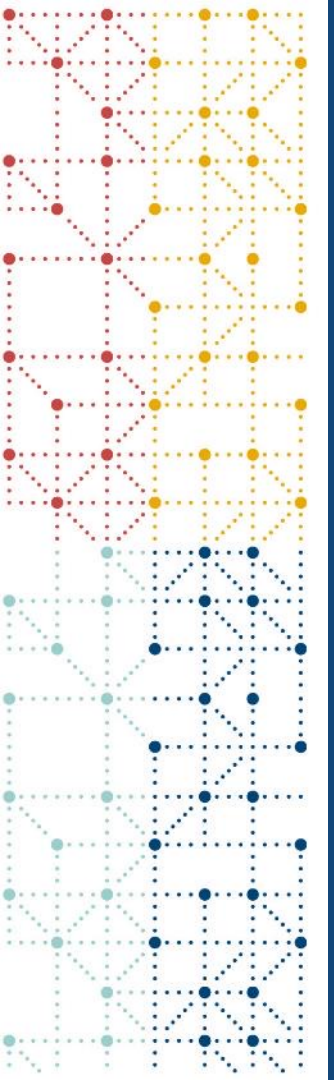
My Experience with the FDA Reviewers and these Additional Requirements / Guidance

MAINLY **CBER** FOR VACCINE SUBMISSION

VERY **DETAILED ASSESSMENT OF OUR SDSP** AND **SAMPLE CRF**

ADHERENCE TO VACCINE TAUGS AND VACCINES TECHNICAL SPECIFICATION GUIDANCE

SOME **REQUESTS COULDN'T BE SATISFIED** E.G., IMPACTING CRF DESIGN (DOCUMENTED DISCUSSION / AGREEMENT IN THE SDSP)



Conclusions

Conclusions

- Be **aware** of these additional guidance and Avoid the **unexpected**
- Impact on Sponsors **Data Governance**
- **CDISC Teams Review** is Needed (Peer Review)
- Still a bit of **variability** across divisions and reviewers
- **Lack of examples** (except NASH and QT)
- **Opportunity** for further standardization

Thank You!

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CDISC Europe Coordinating Committee
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References

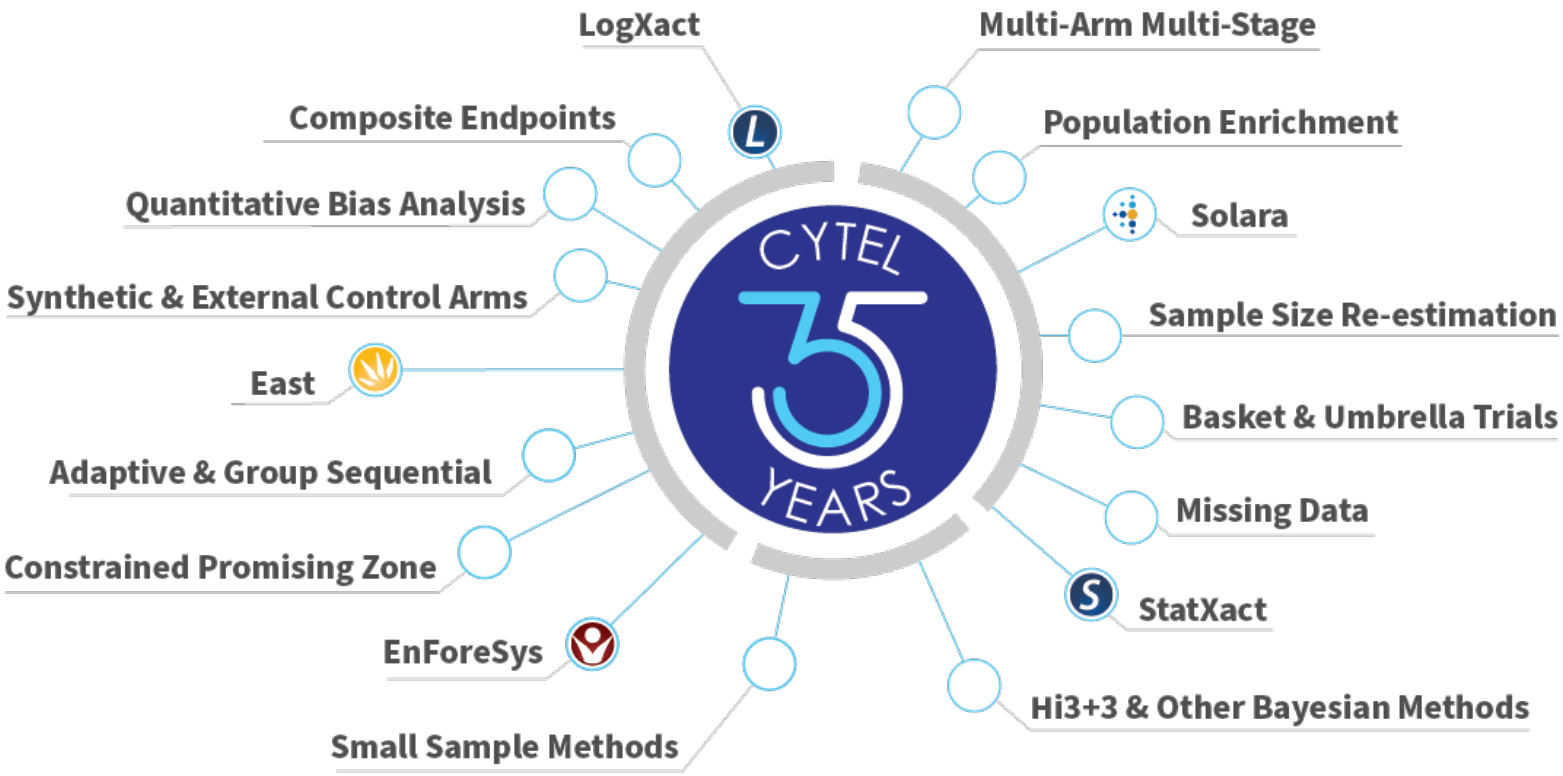
1	"CDISC Therapeutic Areas" https://www.cdisc.org/standards/therapeutic-areas
2	"Therapeutic Area User Guidance – The Hidden Gems" (A. Tinazzi, Cytel Blog, July 2020) https://www.cytel.com/blog/therapeutic-area-user-guidance-the-hidden-gems
3	A Systematic Review of CDISC TAUGs", A. Tinazzi, PharmaSUG-China, 2019, Shanghai https://www.pharmasug.org/proceedings/china2019/DS/Pharmasug-China-2019-DS69.pdf
4	"FDA Study Data Technical Conformance Guidance » (FDA, March 2023) https://www.fda.gov/media/153632/download
5	"Pilot OCE/OOD Safety Team Standard Data Requests" (FDA, February 2021) https://www.fda.gov/media/133252/download
6	"The FDA "Real-Time Oncology Review" Process" (A. Tinazzi, Cytel Blog, November 2021) https://www.cytel.com/blog/the-fda-real-time-oncology-review-process-an-opportunity-challenge-for-sponsors
7	"Challenges with Implementation of New Standards and Guidance – A Sponsor's Experience with the April 2018 CBER Vaccine Guidance", S. VanPelt Nguyen and L. Zhang, PHUSE US Connect 2020 https://www.lexjansen.com/phuse-us/2020/ds/DS05.pdf
8	"Vaccines Technical Specification Guidance" v2.1 (FDA, December 2019) https://www.fda.gov/media/112581/download
9	"Providing Regulatory Submission in Electronic Format" (FDA, December 2014) https://www.fda.gov/media/88120/download
10	"Providing Regulatory Submission in Electronic Format - Standardized Study Data" (FDA, Revision 2 June 2021) https://www.fda.gov/media/82716/download
11	"LB, MB & IS Domain Scope Changes for the SDTMIG v3.4 and Impact on Controlled Terminology" (CDISC webinar) https://www.cdisc.org/events/webinar/lb-mb-domain-scope-changes-sdtmig-v3-4-and-impact-controlled-terminology

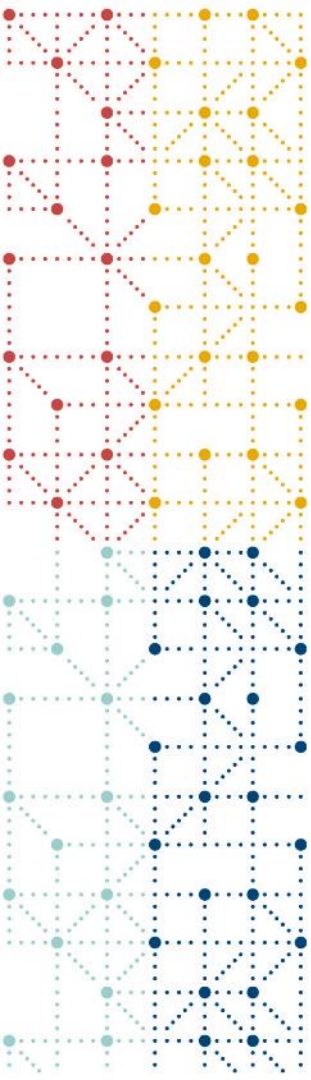
References (cont.)

12	“Data Standards Catalog” (FDA, August 2022) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-catalog-v90
13	“Technical Rejection Criteria for Study Data” (FDA, May 2018) https://www.fda.gov/files/drugs/published/Technical-Rejection-Criteria-for-Study-Data.pdf
14	“Portable Document Format (PDF) Specifications” (FDA, September 2016) https://www.fda.gov/media/76797/download
15	"Electronic Common Technical Document (eCTD)” (FDA, March 2023) https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd
16	“Bioresearch Monitoring Technical Conformance Guide Technical Specifications” (FDA, August 2022) https://www.fda.gov/media/85061/download
17	“Submit an eCTD or Standardized Data Sample to the FDA” (FDA, January 2022) https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda
18	“Providing Regulatory Submissions in Electronic Format - General Considerations” (FDA, January 1999) https://www.fda.gov/media/71200/download
19	“Creating Simplified TS.XPT Files” (FDA, November 2019) https://www.fda.gov/media/132457/download
20	“Model Data Format for submitting pharmacometric data and models” (FDA, August 2021) https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format
21	“Impact of FDA Technical Specifications on CDISC Implementation for NASH Trials”, Cécile Cornou; Henning Pontoppidan, Novo Nordisk A/S CDISC EU Interchange 2022
22	PHUSE “Best Practices for Submission of Event Adjudication Data” (October 2019) https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Best+Practices+for+Submission+of+Event+Adjudication+Data.pdf

Abstract

This presentation aims to raise awareness about the underutilized FDA guidance documents for CDISC implementers. In the presentation we will delve into key topics covered in these additional resources and we will share our experiences with the FDA, and in particular with some of their divisions, commenting on our data packages by referencing these guidance.


LogXact
Multi-Arm Multi-Stage
Composite Endpoints
Population Enrichment
Quantitative Bias Analysis
Solara
Synthetic & External Control Arms
Sample Size Re-estimation
East
Basket & Umbrella Trials
Adaptive & Group Sequential
Missing Data
Constrained Promising Zone
StatXact
EnForeSys
Hi3+3 & Other Bayesian Methods
Small Sample Methods
CYTEL
35
YEARS



Backup Slides

Key Contents

#	FDA Additional Data Standards Guidance References	Content
1	**Vaccines** Technical Specification Guidance v2.1 (Apr 2018 - Dec 2019) https://www.fda.gov/media/112581/download	- CBER[1] OVRR[2] - SDTM - CRF design and mapping recommendations for Reactogenicity data (flat vs nested model) - Vaccines CDISC TAUG
2	**QT Studies** Technical Specification Document v1.0 (Jun 2019) https://www.fda.gov/media/128187/download	- CDER[3] - ADaM e.g., ADEG, ADPC - QT CDISC TAUG
3	Submitting Select Clinical Trial Data Sets for Drugs Intended to Treat **Human Immunodeficiency Virus-1 Infection** v1.0 (Mar 2018) https://www.fda.gov/media/112667/download	- CDER - ADaM e.g., ADAE (non-OCCDS), ADLB (list of main laboratory parameters of interest) ADEFFOUT (ADSL-like focusing on efficacy endpoint) - HIV CDISC TAUG
4	Technical Specifications—Comparative **Clinical Endpoint Bioequivalence Study Analysis Datasets** for Abbreviated New Drug Applications v1.0 (Sep 2018) https://www.fda.gov/media/116187/download	- CDER - ADaM e.g., ADSL and other ADaM specific for each type of study Bioequivalence study
5	Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of **Noncirrhotic Nonalcoholic Steatohepatitis (NASH)** v1.1 (Aug 2021 – Jan 2022) [20] https://www.fda.gov/media/151864/download	- CDER - SDTM (14 domains) Events adjudication recommendations (ZA), Liver Imaging results (ZI) - ADaM (7 domains)

CDISC Topics Covered in Individual Guidance (cont)

Guidance	Topic	Domain	Content Discussed	Additional Details
NASH	SDTM	BE BS MI SUPPMI	BE / BS (collected biopsies material/quality) MI (Histology of liver biopsies) SUPPMI (adequacy of slide assessment)	• Mapping details BEDECOD. • Reference to SDTM PGx 1.0 • Use of MIACPTFL • Full details of MITESTCD with expected results and MITSTDTL (qualifier of MITESTCD) • Terminology for SUPPMI
NASH	SDTM	RS	Disease response to therapy, clinical classification using MELD scoring....	• Precise guidance on how to model a non-standard criterion with suggested TESTCD/TEST • Way of linking related records in LB through use of RELREC and --LNKID
NASH	SDTM	ZI	Results of imaging of liver stenosis, inflammation, etc.	• Reference of SDTMIG-MD to capture device used
NASH	SDTM	ZA	Clinical events and outcomes related to DILI. Like MI with individual assessment of adjudicators	• FA structure, clear instructions on how to set ZAOBJ e.g., DILI or CARDIAC MACE and ZATEST e.g., EVALUATED EVENT ONSET DATE (earliest date). ZACAT for 'FIRST ADJUDICATION' or a 'READJUDICATION' etc. Table with specifications of all variables
NASH	SDTM	DM	Reference start date as 1st treatment	
NASH	SDTM	CM	Particular attention to specific drug lipid-lowering agents, statins, antihypertensive, antidiabetic, thiazolidinediones, vitamin E, and anticoagulants and antiplatelets	
NASH	SDTM	MH	Of particular interest are preexisting medical conditions that may impact NASH disease progression and/or DILI assessment	

CDISC Topics Covered in Individual Guidance (cont)

Guidance	Topic	Domain	Content Discussed	Additional Details
NASH	SDTM	LB	List of expected labs per category	For example, hematology, metabolic, liver parameters, renal parameters, lipid parameters, coagulation, auto immune system. Biomarkers (controlled terminology provided with reference to CDISC-CT)
NASH	SDTM	MB	Serologic test results for hepatitis (hepatitis A, B, C, and E)	Controlled terminology provided with reference to CDISC-CT
NASH	SDTM	SU	Example of a subject who consumes one, regular-sized beer per day may contain the following data points:	
NASH	SDTM	TS	How to refence the FDA NASH guidance	
NASH	SDTM	RELREC	AE/CM BS/MI ZI/PR AE/ZI (for gastroesophageal variceal hemorrhage) AE/DS/DD (for deaths)	
NASH	ADAM	Programs	To be submitted	
NASH	ADAM	ADSL	Copy of variables into other ADaM e.g., demographics…	• Detailed Specifications. • Key baseline variables e.g., Vital signs at baseline DIABL, HRBL, etc. or labs ALTBL and ALTCAT in category, etc. • Concomitant medications, MELD Score
NASH	ADAM	ADAE	Nothing major, apart mentioning use of SMQ	• Sponsor to note in metadata approach of recording multiple records in AE each time the event changes in severity, relationship, etc. then this should be noted in the metadata. Flag record with worst severity. • Derivations of the hepatic injury flags (to be discussed with the FDA)
NASH	ADAM	ADLB	BDS 5 GB nothing major	• All tests and records carried into ADLB. Example provided in appendix
NASH	ADAM	ADDILI	Derived from ADLB	• Example provided in appendix
NASH	ADAM	ADMI	Evaluation of biopsies by evaluator	
NASH	ADAM	ADRS	From LB and RS	

CDISC Topics Covered in Individual Guidance (cont)

Guidance	Topic	Domain	Content Discussed	Additional Details
NASH	ADAM	ADTTE	TTE endpoints	• Sponsors should provide clear explanations in the ADaM define.xml for how AVAL is derived for each parameter. • Time to Histological Progression to Cirrhosis and other TTE
QTC	ADAM	ADEG	TAUG-QT referenced	Example provided
QTC	ADAM	ADPC	Pk parameter	• To facilitate proper mapping of time matched Pk and ECG rows • FDA's QT Interdisciplinary Review Team (IRT)
HIV	ADAM	ADEFFOUT	This is a one-record-per-subject data set that contains a comprehensive set of variables pertaining to the subject and their measures of efficacy Efficacy Outcomes Dataset Ref HIV CDISC TAUG	• TRTDURD for indicating days Variables using underscore, fragment not always used. • Duplicating / Summarizing information from multiple ADAM / SDTM datasets • One record per subject with standard variables from ADSL plus several additional variables to facilitate the statistical and medical review. This includes : additional study/treatment discontinuation variables, changes in background therapies, genotypic and phenotypic data for baseline background regimens, additional background drug indicator, other baseline characteristics such as count of CD4, CD8 at baseline, viral load at baseline and study discontinuation, other summary variables such as any AE ongoing at study end, efficacy measures of Viral Load
HIV	ADAM	ADAE	Flag records that indicated worst toxicity when multiple AE reporting strategy is followed	CDC Class C Event
HIV	ADAM	ADLB	It includes HIV-RNA (viral load) and many other LB parameter	

CDISC Topics Covered in Individual Guidance

Guidance	Topic	Domain	Content Discussed	Additional Details
Bioequivalence	ADAM		• The adhesion study for transdermal delivery systems (TDS) and topical patches • The irritation/sensitization study for transdermal delivery systems (TDS) and topical patches • The comparative clinical endpoint bioequivalence study using the following primary endpoints: lesion count, 100% clearance of all actinic keratosis (AK) lesions, total nasal symptom score, treatment success based on Physician's Global Assessment (PGA) and Psoriasis Area Severity Index (PASI), Intraocular pressure (IOP) and therapeutic cure based on clinical and mycological cures	