CDISC - Harmonisation et pool de bases de données

Julie Le Boulicaut – 15 juin 2023

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Agenda

- Pool de bases de données cliniques
  - Pourquoi et pour qui ?
  - Quand ?
  - Comment ?

- Harmonisation CDISC
  - Structure
  - Mapping
  - Controlled Terminology – code listes

- Retour sur expérience

2

Pourquoi et pour qui pooler des bases de données?

Pourquoi et pour qui pooler des bases de données ?

- Requis règlementaire pour les autorités de santé :
  - ISS, ISE
  - DSUR
  - BI

- Méta-analyse sur données individuelles :
  - Safety recherche de signal
  - Efficacy augmentation de la puissance des analyses

- Autres raisons :
  - Catalogue, outil de requêtes
  - Projet de data visualisation

ISS / ISE : Integrated Summary of Safety / Integrated Summary of Efficacy

- Documents requis par la FDA lors du dépôt d'une demande de nouveau médicament
  - NDA New Drug Application

- Présentation des résultats d'un ou de plusieurs essais cliniques

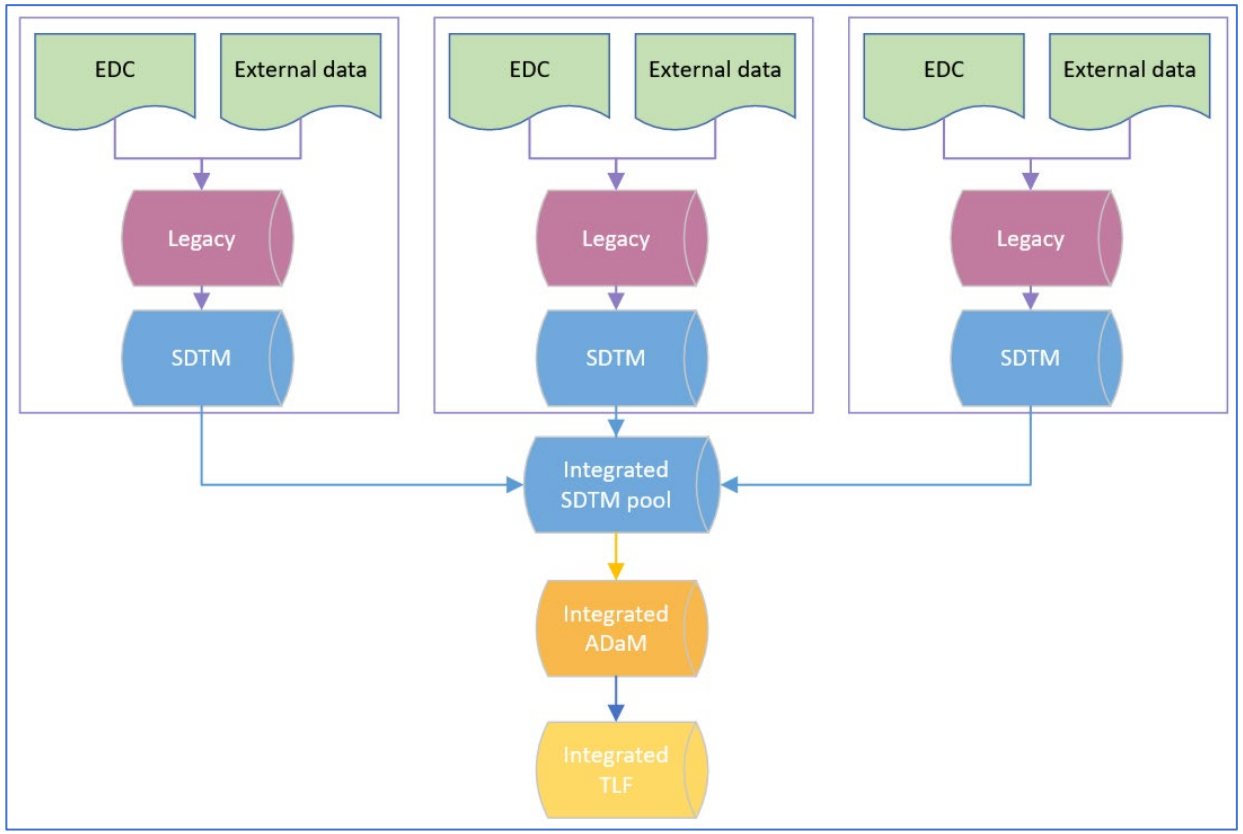
- Une base de données unique est constituée

- Mise à jour annuelle du rapport bénéfice-risque

Quand pooler des bases de données?

Harmonisation CDISC

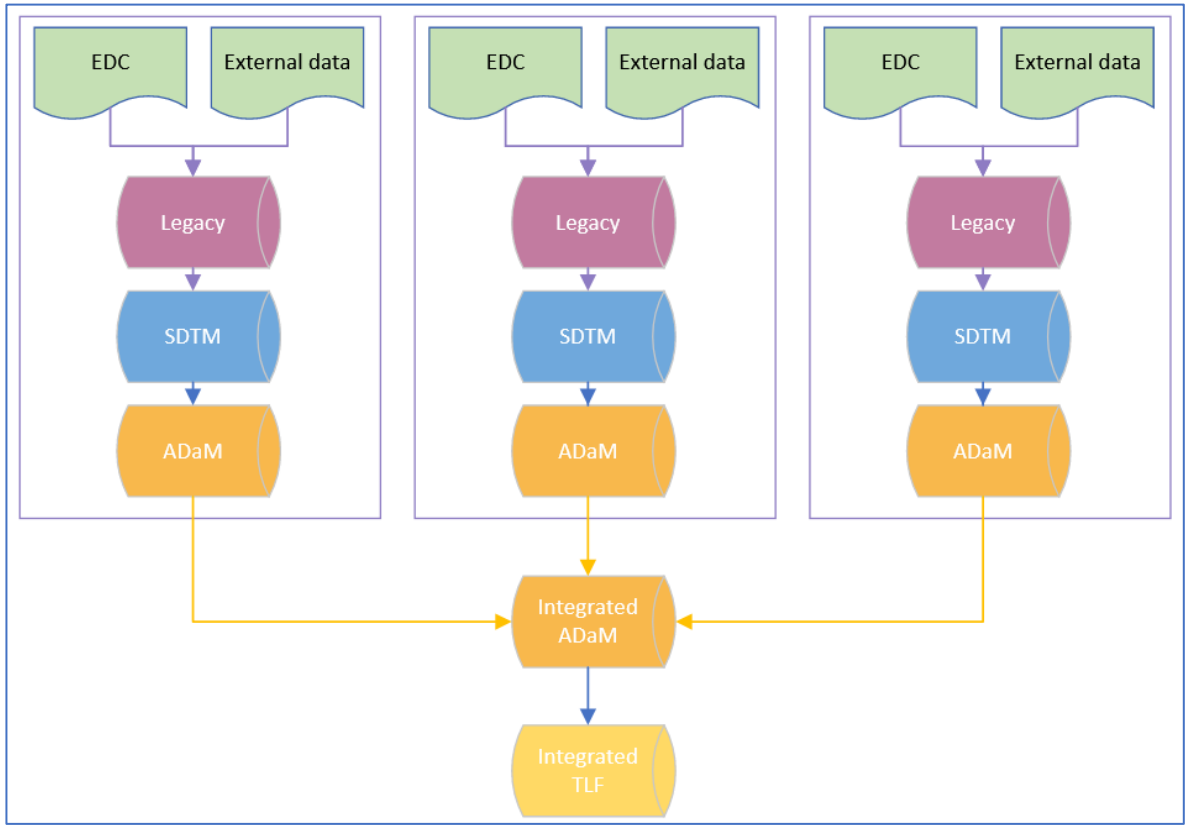
- Pool SDTM ?



Option 1 – Integration Analysis Data Pool from Integrated SDTM Pool

Harmonisation CDISC

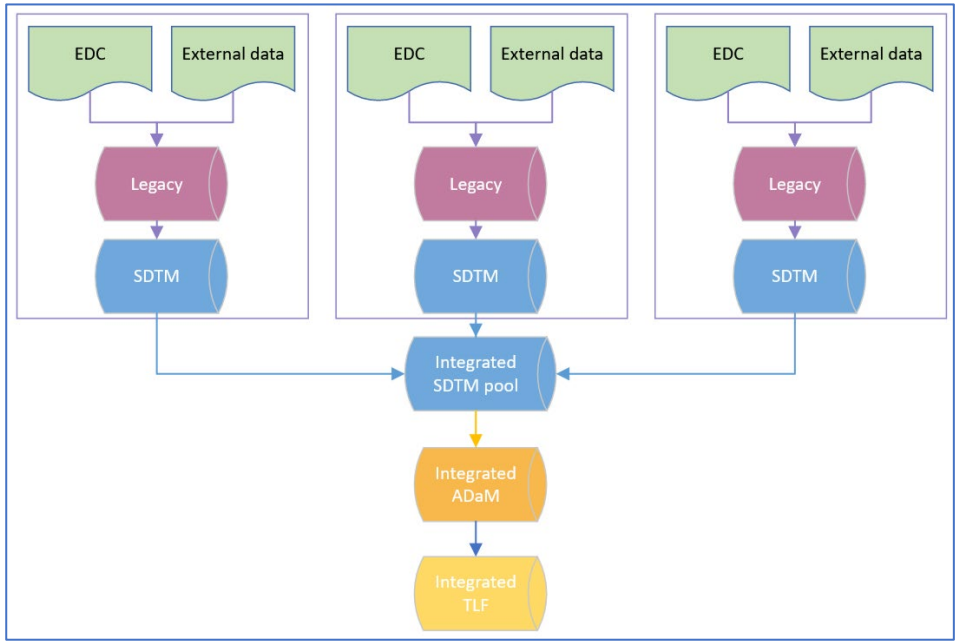
- Pool ADaM?



Option 2 – Integration Analysis Data Pool Using ADaM Data of Individual Studies

Harmonisation – La décision depend de la situation des études individuelles

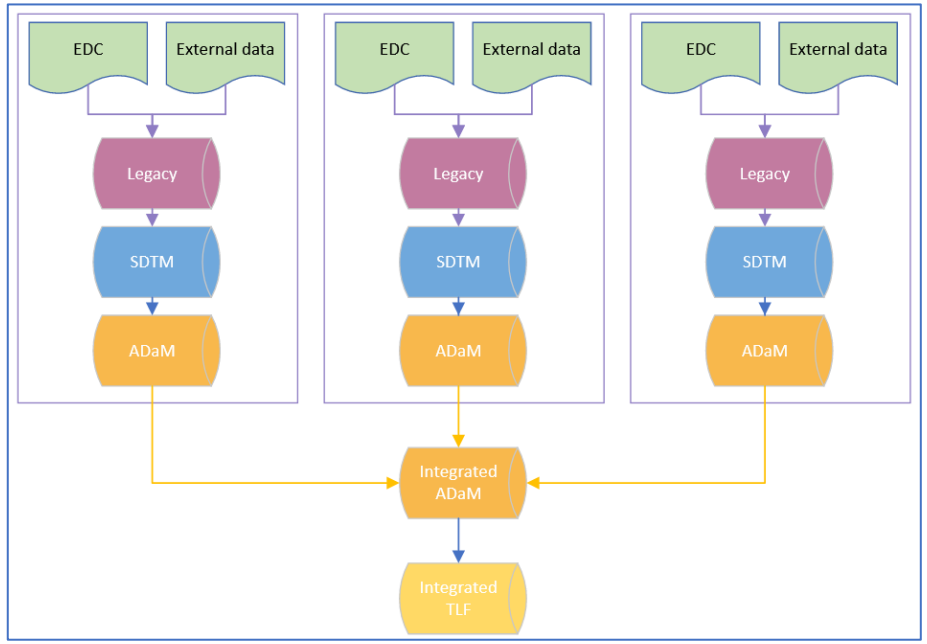
- Pool SDTM



Environnement moins normalisé
Temps et ressources +++

ou

Pool ADaM?



Environnement normalisé
Temps et ressources limités

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Comment pooler des bases de données SDTM?

On ne peut pooler que des structures préalablement harmonisées

Harmonisation CDISC - SDTM

- Qu'avons-nous au départ? CDISC or not CDISC?

- Legacy - héritage
- SDTM
  - Quelle version? Quelles règles de base?
  - Nécessité d'harmoniser une base SDTM vers la base SDTM poolée

Etude	Phase	Format de la base	En cours/Terminée
Etude 1	I Double Blind	Legacy	terminée
Etude 2	II Double Blind	Legacy	terminée
Etude 3	II Double Blind	Legacy	terminée
Etude 4	IIb Double Blind	SDTM CRO 1	terminée
Etude 5	IIb Open label	SDTM CRO 2	en cours
Etude 6	III Double Blind	SDTM CRO 3	en cours
Etude 7	III Double Blind	SDTM CRO 2	en cours

Harmonisation – Structure SDTM

- Names of domains: «**AE** for Adverse Events »

- Structure of domains: «one row per event »

- Names of variables: « start date of AE = **AESTDTC** »

- Format of variables: « start date of AE = **date format ISO 8601** (ex: 2016-08-31T09:00) »

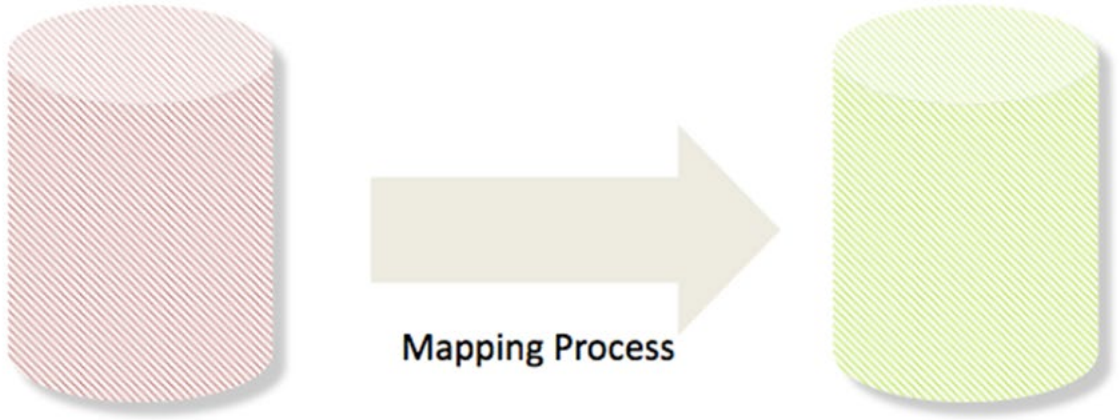
- Sort of variables in a domain: « AE sorted **by study, patient, sequence number** »

- Mandatory and optional variables: « Start date of AE is **mandatory**, location of event is **optional** »

- Names of labels: example « Start date of AE = « ***Start Date/Time of Adverse Event***» »

Harmonisation CDISC

- Mapping – programmation SAS



Sources Datasets
= legacy datasets

Target Datasets: Standard
= CDISC SDTM
= CDISC ADaM

Structure SDTM – principe du mapping

SV – Specification for the SUBJECT VISITS Domain Model

sv.xpt, Subject Visits — Version 3.2,. One record per subject per actual visit.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	SV	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req
VISITNUM	Visit Number	Num		Topic	1. Clinical encounter number. (Decimal numbering may be useful for inserting unplanned visits.) 2. Numeric version of VISIT, used for sorting.	Req
VISIT	Visit Name	Char		Synonym Qualifier	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY as a text description of the clinical encounter.	Perm
VISITDY	Planned Study Day of Visit	Num		Timing	Planned study day of the start of the visit based upon RFSTDTC in Demographics.	Perm
SVSTDTC	Start Date/Time of Visit	Char	ISO 8601	Timing	Start date/time for a Visit.	Exp
SVENDTC	End Date/Time of Visit	Char	ISO 8601	Timing	End date/time of a Visit.	Exp
SVSTDY	Study Day of Start of Visit	Num		Timing	Study day of start of visit relative to the sponsor-defined RFSTDTC.	Perm
SVENDY	Study Day of End of Visit	Num		Timing	Study day of end of visit relative to the sponsor-defined RFSTDTC.	Perm
SVUPDES	Description of Unplanned Visit	Char		Synonym Qualifier	Description of what happened to the subject during an unplanned visit.	Perm

** Indicates variable may be subject to controlled terminology, (Parenthesis indicates CDISC/NCI codelist code value)*

STUDYID	DOMAIN	USUBJID	VISITNUM	VISIT	VISITDY	SVSTDTC	SVENDTC	SVSTDY	SVENDY	SVUPDES
V	SV	V -21-01	1	SCREENING	.	2012-09-13	2012-09-13	-27	-27	
V	SV	V -21-01	2	SCEENING 2	.	2012-09-26	2012-09-26	-14	-14	
V	SV	V -21-01	3	SCREENING 3	.	2012-10-03	2012-10-03	-7	-7	
V	SV	V -21-01	4	DAY 1	.	2012-10-10	2012-10-10	1	1	
V	SV	V -21-01	11	DAY 8	.	2012-10-17	2012-10-17	8	8	
V	SV	V -21-01	25	MONTH 1	.	2012-11-07	2012-11-07	29	29	
V	SV	V -21-01	27	MONTH 3	.	2013-01-09	2013-01-11	92	94	
V	SV	V -21-01	30	MONTH 6	.	2013-04-03	2013-04-22	176	195	
V	SV	V -21-01	33	MONTH 9	.	2013-07-09	2013-07-18	273	282	
V	SV	V -21-01	36	MONTH 12	.	2013-10-09	2013-10-16	365	372	
V	SV	V -21-01	98	END OF STUDY	.	2013-10-16	2013-10-16	372	372	
V	SV	V -21-01	99	FOLLOW-UP	.	2013-10-31	2013-10-31	387	387	

Harmonisation CDISC - SDTM

- Harmoniser la structure mais pas que… le contenu doit être harmonisé également :
  - Controlled Terminology – les codelistes

CDISC SDTM Controlled Terminology,

Source: NCI EVS Terminology Resources website: http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/cdisc

NCI Code	CDISC Submission Value	Codelist Name	CDISC Definition	Codelist Extensible
C66767	ACN	Action Taken with Study Treatment	Terminology specifying changes to the study treatment as a result of an adverse event.	No
C101865	ACSPCAT	Acute Coronary Syndrome Presentation Category	A classification of the presentation of acute coronary syndrome.	No
C66769	AESEV	Severity/Intensity Scale for Adverse Events	A scale that defines the degree or state of disease existing in a patient as a result of the occurrence of an adverse event. (NCI)	No
C66781	AGEU	Age Unit	Those units of time that are routinely used to express the age of a subject.	No
C120521	AVOUTTRT	Anti-Viral Outcome of Treatment	A terminology codelist to describe the anti-viral outcome of treatment.	Yes

Harmonisation CDISC - SDTM

ACN (Action Taken with Study Treatment)

NCI Code: C66767, Codelist extensible: No

C66767	ACN			
NCI Code	**CDISC Submission Value**	**CDISC Synonym**	**CDISC Definition**	**NCI Preferred Term**
C49503	DOSE INCREASED		An indication that a medication schedule was modified by addition; either by changing the frequency, strength or amount. (NCI)	Dose Increased
C49504	DOSE NOT CHANGED		An indication that a medication schedule was maintained. (NCI)	Dose Not Changed
C49505	DOSE REDUCED		An indication that a medication schedule was modified by subtraction, either by changing the frequency, strength or amount. (NCI)	Dose Reduced
C49501	DRUG INTERRUPTED		An indication that a medication schedule was modified by temporarily terminating a prescribed regimen of medication. (NCI)	Drug Interrupted
C49502	DRUG WITHDRAWN		An indication that a medication schedule was modified through termination of a prescribed regimen of medication. (NCI)	Drug Withdrawn
C48660	NOT APPLICABLE	NA;Not Applicable	Determination of a value is not relevant in the current context. (NCI)	Not Applicable
C17998	UNKNOWN	U;Unknown	Not known, not observed, not recorded, or refused. (NCI)	Unknown

Controlled terminology

C66767	ACN
NCI Code	CDISC Submission Value
C49503	DOSE INCREASED
C49504	DOSE NOT CHANGED
C49505	DOSE REDUCED
C49501	DRUG INTERRUPTED
C49502	DRUG WITHDRAWN
C48660	NOT APPLICABLE
C17998	UNKNOWN

- Etude 1 - AE: Action taken
- «None » « Interrupted » « Discontinued Permanently»

Etude 1 modalités	SDTM code liste
	DOSE INCREASED
None	DOSE NOT CHANGED
	DOSE REDUCED
Interrupted	DRUG INTERRUPTED
Discontinued Permanently	DRUG WITHDRAWN
	NOT APPLICABLE
	UNKNOWN

Controlled terminology

C66767	ACN
NCI Code	CDISC Submission Value
C49503	DOSE INCREASED
C49504	DOSE NOT CHANGED
C49505	DOSE REDUCED
C49501	DRUG INTERRUPTED
C49502	DRUG WITHDRAWN
C48660	NOT APPLICABLE
C17998	UNKNOWN

- Etude 2 - AE: Action taken
- no action taken collected
  - Action: value = «Unknown »
  - To document : action taken not collected in CRF

Controlled terminology

C66767	ACN
NCI Code	CDISC Submission Value
C49503	DOSE INCREASED
C49504	DOSE NOT CHANGED
C49505	DOSE REDUCED
C49501	DRUG INTERRUPTED
C49502	DRUG WITHDRAWN
C48660	NOT APPLICABLE
C17998	UNKNOWN

- Etudes 4, 5, 6 - AE: Action taken
- : «Dose Not Changed» « Drug Interrupted» « Drug Withdrawn» « Not Applicable »

Etudes 4, 5, 6 modalités	SDTM code liste
	DOSE INCREASED
Dose Not Changed	DOSE NOT CHANGED
	DOSE REDUCED
Drug Interrupted	DRUG INTERRUPTED
Drug Withdrawn	DRUG WITHDRAWN
Not Applicable	NOT APPLICABLE
	UNKNOWN

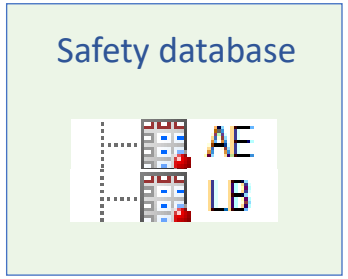
Une expérience… formatrice !

Retour d’expérience

- ISS pour une soumission NDA

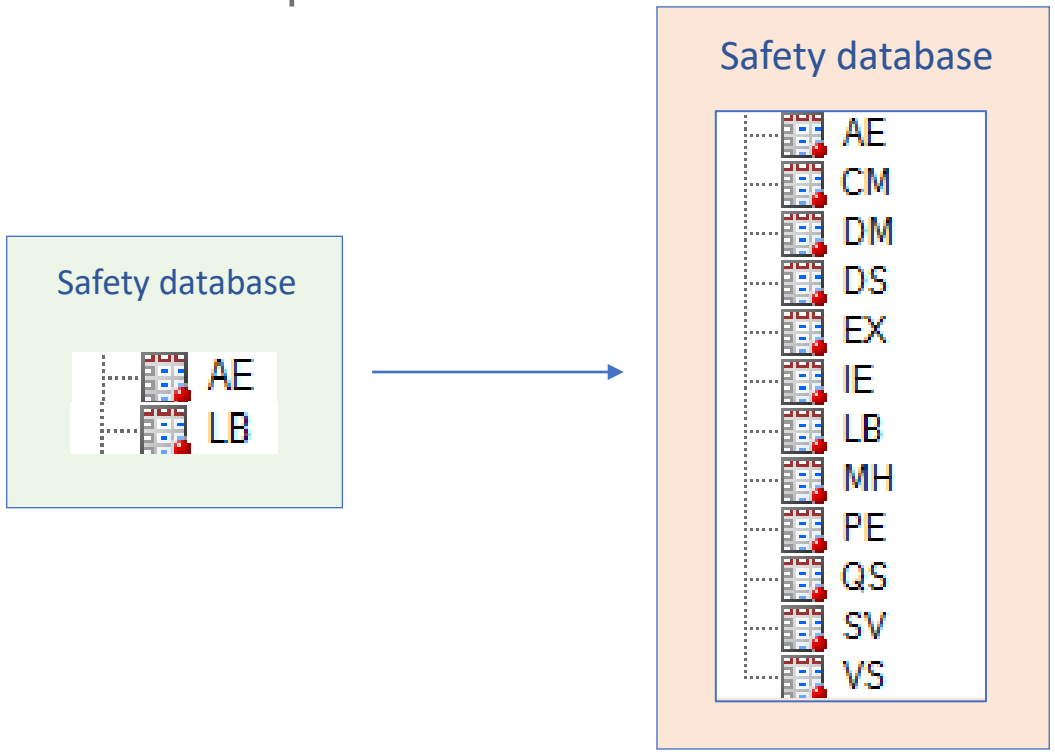
- Démarrage du projet
  - 7 études : 3 terminées / 4 en cours
  - 7 bases de données : 3 legacy / 4 SDTM crées par différentes CROs

- Cahier des charges initial: créer une base safety regroupant AE et lab data



Retour d'expérience

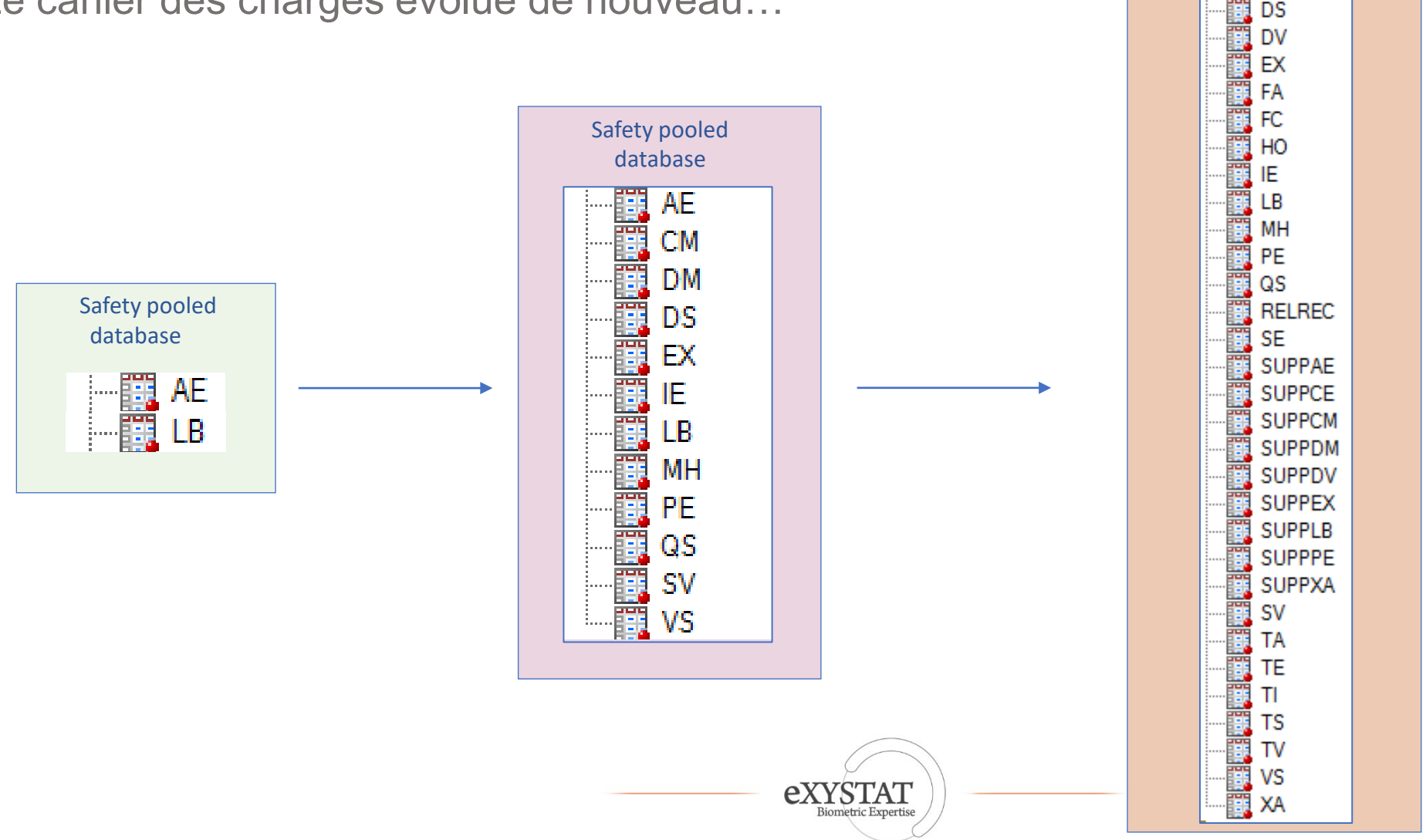
- Le cahier des charges évolue rapidement…



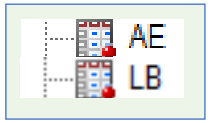
- AE: Adverse Events
- CM: Concomitant Medications
- DM: Demographics
- DS: Disposition
- EX: Exposure
- IE: Inclusion/Exclusion Criteria Not Met
- LB: Laboratory Tests
- MH: Medical History
- PE: Physical Examination
- QS: Questionnaires
- SV: Subject Visits
- VS: Vital Signs

Retour d'expérience

- Le cahier des charges évolue de nouveau…

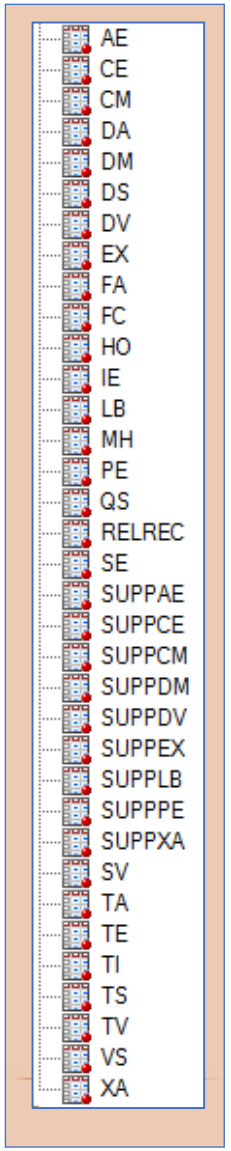


Au démarrage



- Pas de réunion projet
- 2 personnes impliquées chez le sponsor
- Pas de contacts avec les CROs
- Pas de ressource prévue pour valider
- 1ere action = programmation SAS

2 ans après



- Réunions hebdomadaires
- 15 personnes impliquées, tous les services
- Contacts avec les CROs des études en cours
- Contrat spécifique avec une CRO pour valider le pool, 3 ETP pendant 2 mois
- Documentation+++

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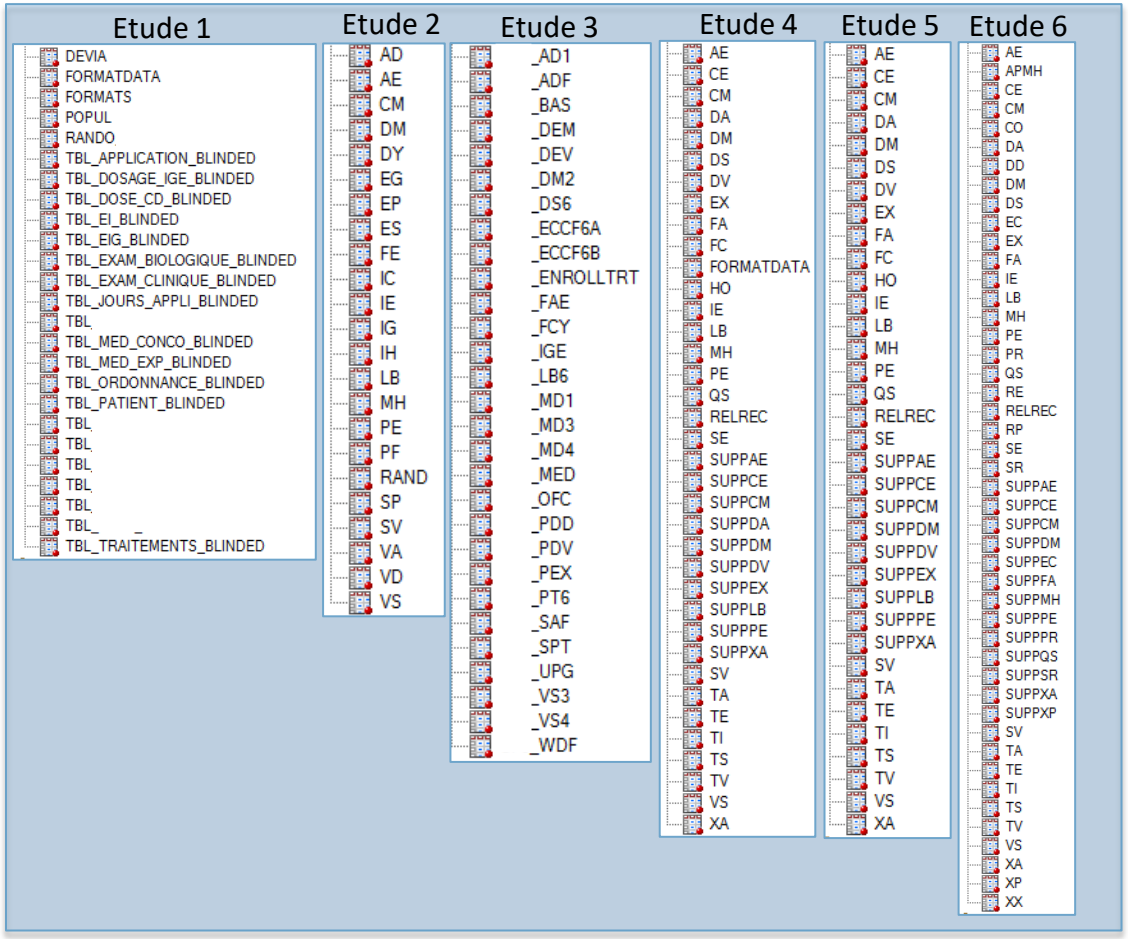
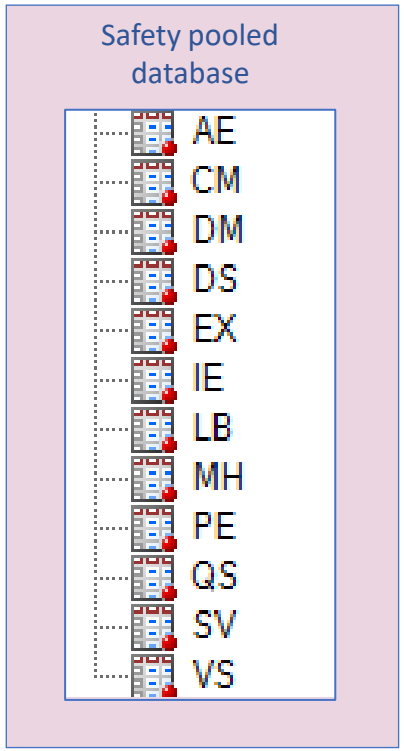
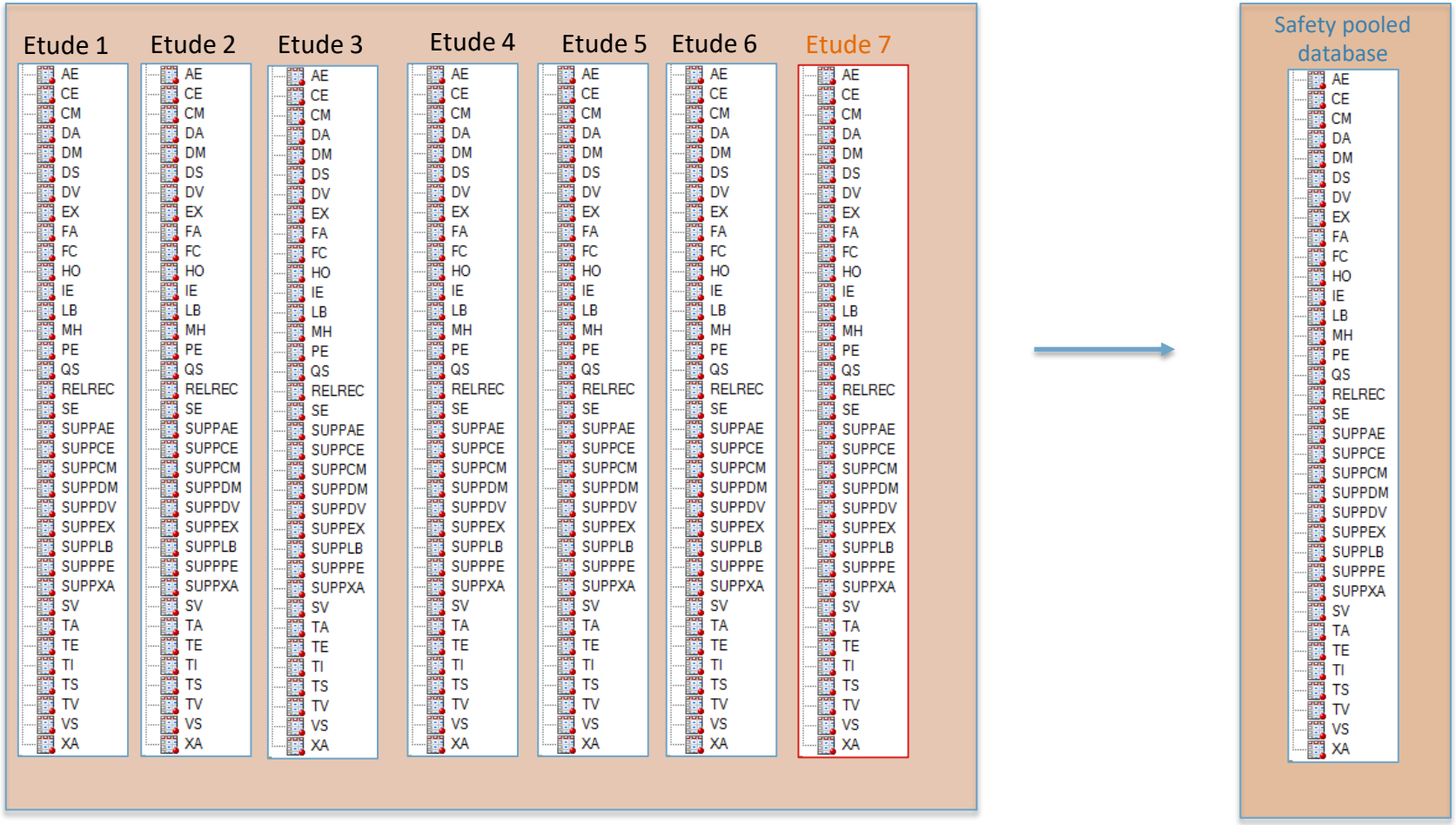
Retour d'expérience





Retour d'expérience



Avec le recul, quelques recommandations

1 - Etudes individuelles: documentation à centraliser

Collecte de la documentation des études individuelles, à minima:

- Protocole
- Blank CRF (pages uniques si possible)
- aCRF
- Data Management Plan
- Convention de codage
- Statistical Analysis Plan

2 – Regarder les bases de données individuelles

Etude	Phase	Format de la base	En cours/Terminée
Etude 1	I Double Blind	Legacy	terminée
Etude 2	II Double Blind	Legacy	terminée
Etude 3	II Double Blind	Legacy	terminée
Etude 4	IIb Double Blind	SDTM CRO 1	terminée
Etude 5	IIb Open label	SDTM CRO 2	en cours
Etude 6	III Double Blind	SDTM CRO 3	en cours
Etude 7	III Double Blind	SDTM CRO 2	en cours

3 - Etudes individuelles: identification des données clés

Identification des données concernées par le pool:

- Responsabilité du sponsor / Annotation « SDTM poolé » des CRF individuels
- « Not submitted » pour les données non concernées par le pool

VS = Vital signs

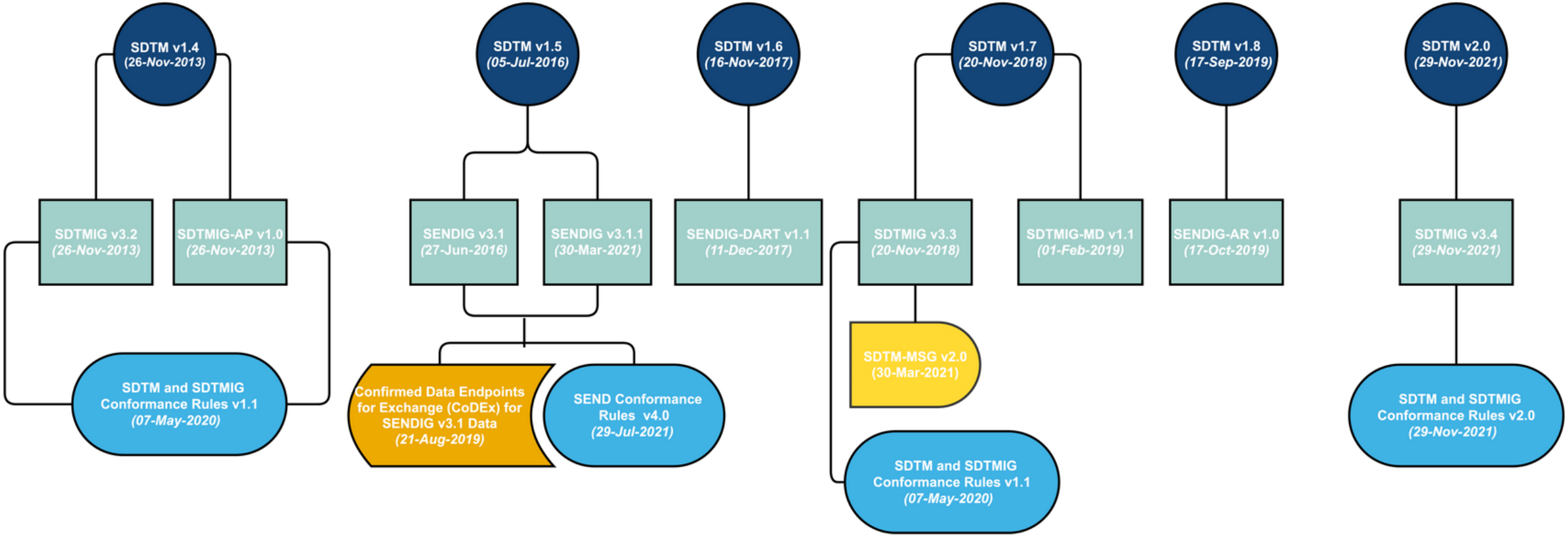
DM = Demographics

Screening Visit 1 (Day -90) [V1]

Demographics [DM]

Patient: *<Patient ID>* Event: *<Visit>*	Investigator: *<Doctor>*
Question	Data Formatting
[DMDOB] Date of Birth	DD-MMM-YYYY *BRTHDTC*
[DMGEN] Gender	_____| GENDER *SEX* [Male]=[Male] [Female]=[Female]
[DMPREGT] Has a Urine Pregnancy Test result been provided?	_____| YESNO(1) *[NOT SUBMITTED]* [Yes]=[Yes] [No]=[No]
[DMPRGRES] Urine Pregnancy Test Result	_____| *[NOT SUBMITTED]* PREGT [Negative]=[Negative] [Positive]=[Positive]
[DMPREOTH] If "No" please specify reason for No pregnancy test results.	_____|(200)"abc" *[NOT SUBMITTED]*
[DMHG] Height in cm *VSORRESU* *VSORRES when VSTESTCD = HEIGHT*	_____|(5) #
[DMWG] Weight in kg *VSORRESU* *VSORRES when VSTESTCD = WEIGHT*	_____|(5) #
[DMRAC] Race of Subject	_____| *RACE* RACE(1)

4 - Versioning – definition d'une stratégie

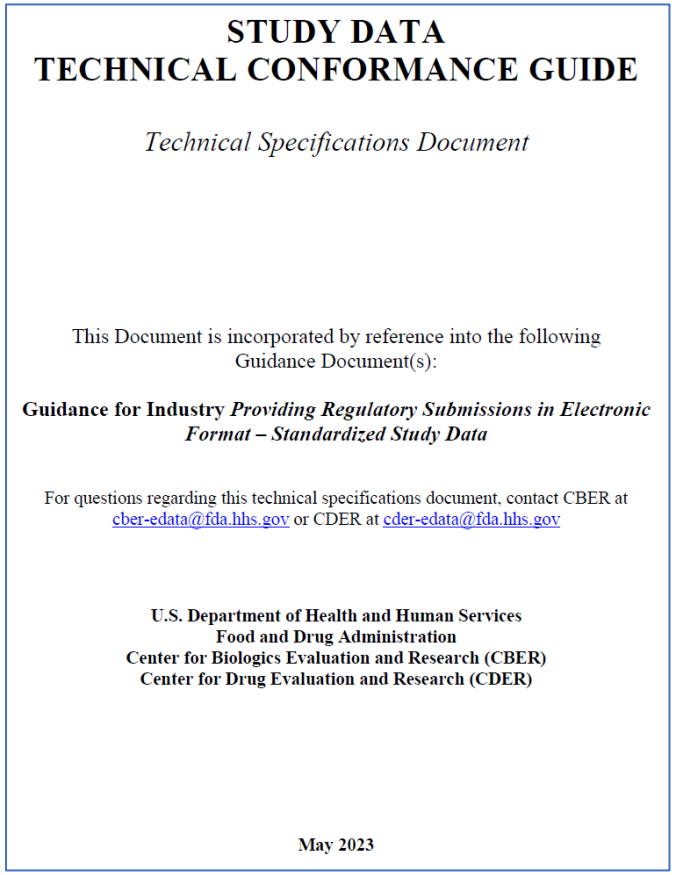


5 – Spécifications SDTM: pour chaque étude individuelle

Rédiger 1 fichier de spécification par étude individuelle, même si la structure initiale est SDTM

Target Standards									Legacy Standards							
	Variables										Variable						
Domain Prefix	Name	Label	Type	Length	Controlled Terms, codelist or format	Role	Origin	Core	Study Name	Dataset Name	Name	Label	Type	Length	Format	Origin	Mapping instruction
DM	STUDYID	Study Identifier	Char	10		Identifier	Protocol	Req			ARACHILD				ARACHILD	Protocol	
DM	DOMAIN	Domain Abbreviation	Char	2	DM	Identifier	Assigned	Req			DM				DM	Assigned	
DM	USUBJID	Unique Subject Identifier	Char	20		Identifier	CRF	Req			NUM_CENTRE/NUM_PAT	N° Centre :/N° Patient	Char/Char	50/2	ARACHILD-XXY	Derived	
DM	SUBJID	Subject Identifier for the Study	Char	10		Topic	Derived	Req			PATIENT	Référence patient :	Char	7		Derived	
DM	RFSTDTC	Subject Reference Start Date/Time	Char	19	ISO 8601	Record Qualifier	CRF	Exp			DT_RANDO					CRF	
DM	RFENDTC	Subject Reference End Date/Time	Char	19	ISO 8601	Record Qualifier	CRF	Exp			DT_SORTIE_ESSAI					CRF	
DM	RFXSTDTC	Date/Time of First Study Treatment	Char	19	ISO 8601	Record Qualifier	CRF	Exp			TBL_PATIENT_BLINDED/DT_RANDO					CRF	
DM	RFXENDTC	Date/Time of Last Study Treatment	Char	19	ISO 8601	Record Qualifier	CRF	Exp			TBL_PATIENT_BLINDED/DT_FIN_TRT_FIN_ETUDE					CRF	
DM	RFICDTC	Date/Time of Informed Consent	Char	19	ISO 8601	Record Qualifier	CRF	Exp			DT_INCL					CRF	
DM	RFPENDTC	Date/Time of End of Participation	Char	19	ISO 8601	Record Qualifier	Derived	Exp									
DM	DTHDTC	Date/Time of Death	Char	19	ISO 8601	Record Qualifier	CRF	Exp			DADEBEIG/HDEBEIG where CODNATEIG=1					Derived	
DM	DTHFL	Subject Death Flag	Char	1	NY	Record Qualifier	Derived	Exp			if CODNATEIG=1					Derived	
DM	SITEID	Study Site Identifier	Char	2		Record Qualifier	Derived	Req			NUM_CENTRE	N°CENTRE:	Char	50		Derived	
DM	INVID	Investigator Identifier	Char	50		Record Qualifier		Perm									
DM	INVNAM	Investigator Name	Char	50		Synonym Qualifier		Perm									
DM	BRTHDTC	Date/Time of Birth	Char	19	ISO 8601	Record Qualifier		Perm			DDN	Date de naissance:	Num	8	DDMMYY	CRF	
DM	AGE	Age	Num	8		Record Qualifier		Exp			AGE = (_RFICDT - _BRTHDT)/365.25;					Derived	
DM	AGEU	Age Units	Char	5	AGEU	Variable Qualifier		Exp			YEARS IF AGE ne .					Assigned	
DM	SEX	Sex	Char	1	SEX	Record Qualifier		Req			SEXE	Sexe:	Num	8	CODE_8_LIST	CRF	
DM	RACE	Race	Char	50	RACE	Record Qualifier		Exp									
DM	ETHNIC	Ethnicity	Char	50	ETHNIC	Record Qualifier		Perm									
DM	ARMCD	Planned Arm Code	Char	20		Record Qualifier		Req			TREAT_GROUP					Derived	
DM	ARM	Description of Planned Arm	Char	80		Synonym Qualifier		Req			TREAT_GROUP					Derived	
DM	ACTARMCD	Actual Arm Code	Char	20		Record Qualifier		Req			TREAT_GROUP					Derived	
DM	ACTARM	Description of Actual Arm	Char	80		Synonym Qualifier		Req			TREAT_GROUP					Derived	
DM	COUNTRY	Country	Char	3	COUNTRY ISO 3166	Record Qualifier		Req			FRA					Assigned	
DM	DMDTC	Date/Time of Collection	Char	19	ISO 8601	Timing		Perm			DT_INCL					CRF	
DM	DMDY	Study Day of Collection	Char	8		Timing		Perm			D_INCL - DT_RANDO					CRF	

6 - Codage MedDRA, WhoDD, CTC-AE



STUDY DATA
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

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

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

May 2023

Importance d'harmoniser les versions de dictionnaires

Chapter 6.3.1.1. *"To avoid potential confusion or incorrect results, the preparation of the adverse event dataset for the ISS should include MedDRA terms from the most current version of MedDRA at the time that data across studies are pooled. The reason for an ISS based on a single version of MedDRA is that reviewers often analyze adverse events across studies, including the use of Standardized MedDRA Queries."*

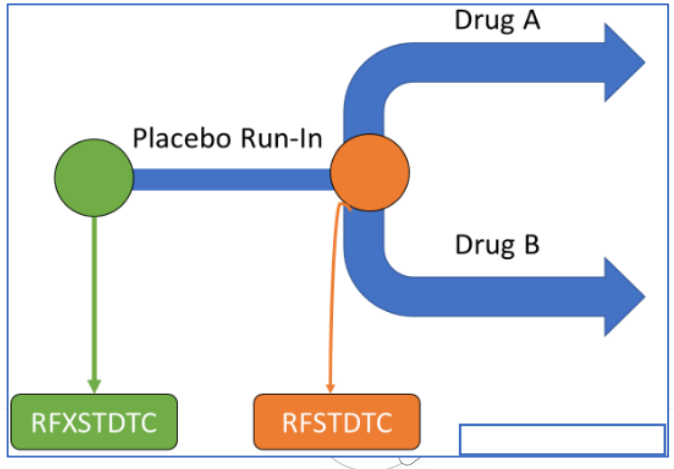
Study	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Coding dictionary versions (MedDRA/ Whodrug)	MedDRA V16.1 WhoDD Sept 2013, B2 format	MedDRA V15.0, V15.1, V16.0, V16.1, V17.0, V17.1, V18.0	?	MedDRA V15.0 WHODD 2012, March	MedDRA V18.1 WHODD 2016, March	MedDRA V19.1 WHODD 2016, Sept (with updates every 6 month)

7 - Définition des variables de référence et des dérivations

- RFSTDTC/RFENDTC :
  - Subject Reference Start/End Date/Time = date de début / date de fin du traitement à l'étude

- RFXSTDTC/RFXENDTC :
  - Date/Time of First/Last Study Treatment = date de début / date de fin parmi tous les enregistrements présents dans le domaine EX (Exposure)

- RFSTDTC/RFXSTDTC et RFENDTC/ RFXENDTC sont souvent équivalents. La différence est que RFSTDTC/RFENDTC sont restreintes au traitement à l'étude



8 - Harmonisation des périodes – Domaine TE/SE

Etude individuelle

ETCD	ELEMENT
100	100 UG
250	250 UG
50	50 UG
FU	FOLLOW-UP
P	PLACEBO
SCRN	SCREENING

Pool

ETCD	ELEMENT	Studies
100	100 UG	2 / 3 / 4 / 5
100a	100 UG PER 24 HOURS	1
100b	100 UG PER 48 HOURS	1
20a	20 UG PER 24 HOURS	1
20b	20 UG PER 48 HOURS	1
250	250 UG	3 / 4 / 5 / 6 / 7
250a	250 UG PER 24 HOURS	1
250b	250 UG PER 48 HOURS	1
50	50 UG	3 / 4
500a	500 UG PER 24 HOURS	1
500b	500 UG PER 48 HOURS	1
FU	FOLLOW-UP	1 / 2 / 3 / 4 / 6 / 7
OPLB12M	100 UG OPEN LABEL	2
OPLB18ME	100 UG OPEN LABEL - EXTENSION 18M	2
OPLB24ME	100 UG OPEN LABEL - EXTENSION 24M	2
OPLB30M	250 UG OPEN LABEL	7
OPLB36M	250 UG OPEN LABEL	7
P	PLACEBO	1 / 2 / 3 / 5 / 6 / 7
SCRN	SCREENING	1 / 2 / 3 / 4 / 5 / 6 / 7

9 - Harmonisation des bras de traitement – domaine TA/DM

ARMCD	ARM	Studies
100	PRODUCT 100 UG	2 / 3 / 5
100-100-250	PRODUCT 100 UG-PRODUCT 100 UG-PRODUCT 250 UG	4
100-250-250	PRODUCT 100 UG-PRODUCT 250 UG-PRODUCT 250 UG	4
100a	PRODUCT 100 UG PER 24 HOURS	1
100b	PRODUCT 100 UG PER 48 HOURS	1
20a	PRODUCT 20 UG PER 24 HOURS	1
20b	PRODUCT 20 UG PER 48 HOURS	1
250	PRODUCT 250 UG	3 / 4 / 6 / 7
250-250-250	PRODUCT 250 UG-PRODUCT 250 UG-PRODUCT 250 UG	4
250a	PRODUCT 250 UG PER 24 HOURS	1
250b	PRODUCT 250 UG PER 48 HOURS	1
50	PRODUCT 50 UG	3
50-250-250	PRODUCT 50 UG-PRODUCT 250 UG-PRODUCT 250 UG	4
50-50-250	PRODUCT 50 UG-PRODUCT 50 UG-PRODUCT 250 UG	4
500a	PRODUCT 500 UG PER 24 HOURS	1
500b	PRODUCT 500 UG PER 48 HOURS	1
PLACEBO	PLACEBO	1 / 2 / 3 / 5 / 6 / 7
PLACEBO-100-250	PLACEBO-PRODUCT 100 UG-PRODUCT 250 UG	4
PLACEBO-250-250	PLACEBO-PRODUCT 250 UG-PRODUCT 250 UG	4
PLACEBO-50-250	PLACEBO-PRODUCT 50 UG-PRODUCT 250 UG	4

10 - Harmonisation des visites – domaine TV/SV

Etude 1	TV	10	SCREENING 1
Etude 1	TV	41	DAY 1
Etude 1	TV	42	DAY 2
Etude 1	TV	43	DAY 3
Etude 1	TV	50	DAY 8
Etude 1	TV	51	WEEK 2
Etude 1	TV	510	END OF STUDY
Etude 1	TV	300	UNSCH
Etude 2	TV	10	SCREENING 1
Etude 2	TV	40	BASELINE - START OF TREATMENT
Etude 2	TV	50	DAY 8
Etude 2	TV	60	MONTH 1
Etude 2	TV	70	MONTH 2
Etude 2	TV	80	MONTH 3
Etude 2	TV	90	MONTH 6
Etude 2	TV	90.10	MONTH 6 + 7 DAYS
Etude 2	TV	91	MONTH 7
Etude 2	TV	100	MONTH 9
Etude 2	TV	110	MONTH 12
Etude 2	TV	120	MONTH 15
Etude 2	TV	130	MONTH 18
Etude 3	TV	10	SCREENING 1
Etude 3	TV	20	SCREENING 2
Etude 3	TV	30	SCREENING 3
Etude 3	TV	41	DAY 1
Etude 3	TV	50	DAY 8
Etude 3	TV	60	MONTH 1
Etude 3	TV	80	MONTH 3
Etude 3	TV	90	MONTH 6
Etude 3	TV	100	MONTH 9
Etude 3	TV	110	MONTH 12
Etude 3	TV	510	END OF STUDY
Etude 3	TV	600	FOLLOW-UP
Etude 4	TV	30.10	BASELINE - VIPES BASELINE
Etude 4	TV	41	DAY 1
Etude 4	TV	60	MONTH 1
Etude 4	TV	90	MONTH 6
Etude 4	TV	110	MONTH 12
Etude 4	TV	110.30	MONTH 12 + 7 DAYS
Etude 4	TV	130	MONTH 18
Etude 4	TV	130.10	MONTH 18 + 2 WEEKS
Etude 4	TV	150	MONTH 24
Etude 4	TV	150.10	MONTH 24 + 7 DAYS
Etude 4	TV	160	MONTH 26
Etude 4	TV	160.10	MONTH 26 + 7 DAYS
Etude 4	TV	510	END OF STUDY
Etude 5	TV	10	SCREENING 1
Etude 5	TV	40	BASELINE - START OF TREATMENT
Etude 5	TV	41	DAY 1
Etude 5	TV	42	DAY 2
Etude 5	TV	51	WEEK 2
Etude 5	TV	52	WEEK 3
Etude 5	TV	60	MONTH 1
Etude 5	TV	70	MONTH 2
Etude 5	TV	80	MONTH 3
Etude 5	TV	80.10	MONTH 4
Etude 5	TV	80.20	MONTH 5
Etude 5	TV	90	MONTH 6
Etude 5	TV	100	MONTH 9
Etude 5	TV	110	MONTH 12
Etude 5	TV	110.10	DAY 01 - POST WEEK 52
Etude 5	TV	110.20	DAY 02 - POST WEEK 52
Etude 5	TV	110.40	WEEK 2 - POST WEEK 52
Etude 5	TV	110.50	WEEK 3 - POST WEEK 52
Etude 5	TV	110.60	WEEK 4 - POST WEEK 52
Etude 5	TV	130	MONTH 18
Etude 5	TV	150	MONTH 24
Etude 5	TV	170	MONTH 30

	VISITNUM	VISIT
Etude 1	1	V1 (Sélection)
Etude 1	2	V2 (Randomisation)
Etude 1	3	V3 (J8)
Etude 1	4	V4 (M1)
Etude 1	5	V5 (M2)
Etude 1	6	V6 (M3-M4)
Etude 1	7	V7 (M6)
Etude 1	8	V8 (M6+7)
Etude 1	9	V9 (M7)
Etude 1	10	V10 (M9)
Etude 1	11	V11 (M12)
Etude 1	12	V12 (M15)
Etude 1	13	V13 (M18)
Etude 1	14	Contact 1 (M21)
Etude 1	15	V14 (M24)
Etude 1	16	Contact 2 (M27)
Etude 1	17	V15 (M30)
Etude 1	18	Contact 3 (M33)
Etude 1	19	V16 (M36)
Etude 1	20	V17 (M37)
Etude 1	21	V18 (M39)
Etude 1	22	V20 (M42)
Etude 1	23	V21 (M43)
Etude 1	24	V22 (M45)

	VISITNUM	VISIT	
Etude 5	10	VISIT 1	START OF SCREENING
Etude 5	10.01	VISIT 1 - UNSCHELDULED 1	
Etude 5	10.02	VISIT 1 - UNSCHELDULED 2	
Etude 5	10.03	VISIT 1 - UNSCHELDULED 3	
Etude 5	10.04	VISIT 1 - UNSCHELDULED 4	
Etude 5	20	VISIT 2	UP TO 2 DAYS BEFORE
Etude 5	20.01	VISIT 2 - UNSCHELDULED 1	
Etude 5	20.02	VISIT 2 - UNSCHELDULED 2	
Etude 5	30	VISIT 3	UP TO 1 DAY BEFORE START OF TRT
Etude 5	30.01	VISIT 3 - UNSCHELDULED 1	
Etude 5	30.02	VISIT 3 - UNSCHELDULED 2	
Etude 5	40	VISIT 4	START OF TREATMENT
Etude 5	40.01	VISIT 4 - UNSCHELDULED 1	
Etude 5	40.02	VISIT 4 - UNSCHELDULED 2	
Etude 5	50	VISIT 5	8 DAYS AFTER START OF TREATMENT
Etude 5	50.01	VISIT 5 - UNSCHELDULED 1	
Etude 5	50.02	VISIT 5 - UNSCHELDULED 2	
Etude 5	60	VISIT 6	1 MONTH AFTER START OF TREATMENT
Etude 5	60.01	VISIT 6 - UNSCHELDULED 1	
Etude 5	60.02	VISIT 6 - UNSCHELDULED 2	
Etude 5	70	VISIT 7	3 MONTHS AFTER START OF TREATMENT
Etude 5	70.01	VISIT 7 - UNSCHELDULED 1	
Etude 5	70.02	VISIT 7 - UNSCHELDULED 2	
Etude 5	80	VISIT 8	6 MONTHS AFTER START OF TREATMENT
Etude 5	80.01	VISIT 8 - UNSCHELDULED 1	
Etude 5	80.02	VISIT 8 - UNSCHELDULED 2	
Etude 5	90	VISIT 9	9 MONTHS AFTER START OF TREATMENT
Etude 5	90.01	VISIT 9 - UNSCHELDULED 1	
Etude 5	90.02	VISIT 9 - UNSCHELDULED 2	
Etude 5	100	VISIT 10	12 MONTHS AFTER START OF TREATMENT
Etude 5	100.01	VISIT 10 - UNSCHELDULED 1	
Etude 5	100.02	VISIT 10 - UNSCHELDULED 2	
Etude 5	110	VISIT 11	LAST DAY OF TREATMEI
Etude 5	110.01	VISIT 11 - UNSCHELDULED 1	
Etude 5	110.02	VISIT 11 - UNSCHELDULED 2	
Etude 5	119	EARLY TERMINATION	TREATMENT DISCONTINUED EARLY
Etude 5	120	VISIT 12	2 WEEKS AFTER START OF FOLLOW-UP
Etude 5	120.1	VISIT 12 - UNSCHELDULED 1	

	VISITNUM	VISIT
Etude 2	00	Screening
Etude 2	01	Baseline
Etude 2	02	Day 01
Etude 2	03	Day 02
Etude 2	04	02 Weeks
Etude 2	05	03 Weeks
Etude 2	06	04 Weeks
Etude 2	06A	08 Weeks
Etude 2	07	12 Weeks
Etude 2	07A	16 Weeks
Etude 2	07B	20 Weeks
Etude 2	08	24 Weeks
Etude 2	09	36 Weeks
Etude 2	10	52 Weeks
Etude 2	10AA	Day 01 post W52
Etude 2	10BB	Day 02 post W52
Etude 2	10CC	02 Weeks post W52
Etude 2	10DD	03 Weeks post W52
Etude 2	10EE	04 Weeks post W52
Etude 2	11	78 Weeks
Etude 2	12	104 Weeks
Etude 2	13	130 Weeks
Etude 2	C02	Crossover C02
Etude 2	C03	Crossover C03
Etude 2	C04	Crossover C04
Etude 2	C05	Crossover C05
Etude 2	C06	Crossover C06
Etude 2	C07	Crossover C07
Etude 2	C08	Crossover C08
Etude 2	C09	Crossover C09
Etude 2	C10	Crossover C10
Etude 2	C11	Crossover C11
Etude 2	C12	Crossover C12
Etude 2	C13	Crossover C13
Etude 2	F01	1 month post final OFC (phone assessment)
Etude 2	F02	2 months post final OFC (phone assessment)
Etude 2	F03	3 months post final OFC (phone assessment)
Etude 2	F04	4 months post final OFC (phone assessment)

M12+7	100.10	
	100.11	
	100.12	

	VISITNUM	VISIT	
Etude 3	1	Visit 1 Screening (Day -28)	
Etude 3	2	Visit 2 Screening (Day -21)	
Etude 3	3	Visit 3 Screening	
Etude 3	4	Visit 4 (Day 1)	40
Etude 3	5	Visit 5 (Day 8)	
Etude 3	6	Visit 6 (Month 1)	
Etude 3	7	Visit 7 (Month 3)	
Etude 3	8	Visit 8 (Month 6)	
Etude 3	9	Visit 9 (Month 9)	
Etude 3	10	Visit 10 (Month 12)	
Etude 3	11	Visit 11 (End of Study)	100.1
Etude 3	12	Visit 12 (Follow-up)	
Etude 3	99	Unscheduled	

	VISITNUM	VISIT	
Etude 6	10	VISIT 1	
Etude 6	10.01	VISIT 1 - UNSCHELDULED 1	START OF SCREENING
Etude 6	10.02	VISIT 1 - UNSCHELDULED 2	
Etude 6	10.03	VISIT 1 - UNSCHELDULED 3	
Etude 6	20	VISIT 2	START OF TREATMENT
Etude 6	20.01	VISIT 2 - UNSCHELDULED 1	
Etude 6	20.02	VISIT 2 - UNSCHELDULED 2	
Etude 6	20.03	VISIT 2 - UNSCHELDULED 3	
Etude 6	30	VISIT 3	8 DAYS AFTER START OF TREATMENT
Etude 6	30.01	VISIT 3 - UNSCHELDULED 1	
Etude 6	30.02	VISIT 3 - UNSCHELDULED 2	
Etude 6	30.03	VISIT 3 - UNSCHELDULED 3	
Etude 6	40	VISIT 4	1 MONTH AFTER START OF TREATMENT
Etude 6	40.01	VISIT 4 - UNSCHELDULED 1	
Etude 6	40.02	VISIT 4 - UNSCHELDULED 2	
Etude 6	40.03	VISIT 4 - UNSCHELDULED 3	
Etude 6	50	VISIT 5	3 MONTHS AFTER START OF TREATMENT
Etude 6	50.01	VISIT 5 - UNSCHELDULED 1	
Etude 6	50.02	VISIT 5 - UNSCHELDULED 2	
Etude 6	50.03	VISIT 5 - UNSCHELDULED 3	
Etude 6	60	VISIT 6	6 MONTHS AFTER START OF TREATMENT
Etude 6	60.01	VISIT 6 - UNSCHELDULED 1	
Etude 6	60.02	VISIT 6 - UNSCHELDULED 2	
Etude 6	60.03	VISIT 6 - UNSCHELDULED 3	
Etude 6	70	VISIT 7	7 MONTHS AFTER START OF TREATMENT
Etude 6	70.01	VISIT 7 - UNSCHELDULED 1	
Etude 6	70.02	VISIT 7 - UNSCHELDULED 2	
Etude 6	70.03	VISIT 7 - UNSCHELDULED 3	
Etude 6	80	VISIT 8	9 MONTHS AFTER START OF TREATMENT
Etude 6	80.01	VISIT 8 - UNSCHELDULED 1	
Etude 6	80.02	VISIT 8 - UNSCHELDULED 2	
Etude 6	80.03	VISIT 8 - UNSCHELDULED 3	
Etude 6	90	VISIT 9	12 MONTHS AFTER START OF TREATMENT
Etude 6	90.01	VISIT 9 - UNSCHELDULED 1	
Etude 6	90.02	VISIT 9 - UNSCHELDULED 2	
Etude 6	90.03	VISIT 9 - UNSCHELDULED 3	
Etude 6	90.04	VISIT 9 - UNSCHELDULED 4	
Etude 6	100	VISIT 10	15 MONTHS AFTER START OF TREATMENT
Etude 6	100.01	VISIT 10 - UNSCHELDULED 1	
Etude 6	100.02	VISIT 10 - UNSCHELDULED 2	
Etude 6	100.03	VISIT 10 - UNSCHELDULED 3	
Etude 6	110	VISIT 11	18 MONTHS AFTER START OF TREATMENT
Etude 6	110.01	VISIT 11 - UNSCHELDULED 1	
Etude 6	110.02	VISIT 11 - UNSCHELDULED 2	
Etude 6	110.03	VISIT 11 - UNSCHELDULED 3	
Etude 6	120	VISIT 12	24 MONTHS AFTER START OF TREATMENT
Etude 6	120.1	VISIT 12 - UNSCHELDULED 1	
Etude 6	120.2	VISIT 12 - UNSCHELDULED 2	
Etude 6	120.3	VISIT 12 - UNSCHELDULED 3	
Etude 6	130	VISIT 13	30 MONTHS AFTER START OF TREATMENT
Etude 6	130.01	VISIT 13 - UNSCHELDULED 1	

	VISITNUM	VISIT
Etude 4	-1.5	VIPES Baseline (Day 1)
Etude 4	-1	VIPES Baseline
Etude 4	-1	VIPES Baseline (+7 Days)
Etude 4	1	Day 1
Etude 4	1.5	Day 1 (+7 Days)
Etude 4	2	Month 1
Etude 4	3	Month 6
Etude 4	4	Month 12
Etude 4	5	Month 12 (+7 Days)
Etude 4	6	Month 18
Etude 4	6.5	Month 18 (+ 2 Weeks)
Etude 4	7	Month 24
Etude 4	8	Month 24 (+7 Days)
Etude 4	9	Month 26
Etude 4	10	Month 26 (+7 Days)
Etude 4	11	End of Study (discontinued)
Etude 4	99	Unscheduled

POOLED DATABASE

VISITNUM	VISIT
10	SCREENING 1
10.01	SCREENING 1 - UNSCH 1
10.02	SCREENING 1 - UNSCH 2
10.03	SCREENING 1 - UNSCH 3
10.04	SCREENING 1 - UNSCH 4
20	SCREENING 2
20.01	SCREENING 2 - UNSCH 1
20.02	SCREENING 2 - UNSCH 2
20.03	SCREENING 2 - UNSCH 3
30	SCREENING 3
30.01	SCREENING 3 - UNSCH 1
30.02	SCREENING 3 - UNSCH 2
30.10	BASELINE - VIPES BASELINE
40	BASELINE - START OF TREATMENT
40.01	BASELINE - UNSCH 1
40.02	BASELINE - UNSCH 2
40.03	BASELINE - UNSCH 3
41	DAY 1
42	DAY 2
43	DAY 3
50	DAY 8
50.01	DAY 8 - UNSCH 1
50.02	DAY 8 - UNSCH 2
50.03	DAY 8 - UNSCH 3
51	WEEK 2
52	WEEK 3
60	MONTH 1
60.01	MONTH 1 - UNSCH 1
60.02	MONTH 1 - UNSCH 2
60.03	MONTH 1 - UNSCH 3
70	MONTH 2
80	MONTH 3
80.01	MONTH 3 - UNSCH 1
80.02	MONTH 3 - UNSCH 2
80.03	MONTH 3 - UNSCH 3
80.10	MONTH 4
80.20	MONTH 5
90	MONTH 6
90.01	MONTH 6 - UNSCH 1
90.02	MONTH 6 - UNSCH 2
90.03	MONTH 6 - UNSCH 3
90.10	MONTH 6 + 7 DAYS
91	MONTH 7
91.01	MONTH 7 - UNSCH 1
91.02	MONTH 7 - UNSCH 2
91.03	MONTH 7 - UNSCH 3
92	MONTH 7,5
93	MONTH 8
100	MONTH 9
100.01	MONTH 9 - UNSCH 1
100.02	MONTH 9 - UNSCH 2
100.03	MONTH 9 - UNSCH 3
100.04	MONTH 9 - UNSCH 4
101	MONTH 10
102	MONTH 11
110	MONTH 12
110.01	MONTH 12 - UNSCH 1
110.02	MONTH 12 - UNSCH 2
110.03	MONTH 12 - UNSCH 3
110.04	MONTH 12 - UNSCH 4
110.10	DAY 01 - POST WEEK 52
110.20	DAY 02 - POST WEEK 52
110.30	MONTH 12 + 7 DAYS
	MONTH 12 + 7 DAYS - UNSCH 1
	MONTH 12 + 7 DAYS - UNSCH 2
110.40	WEEK 2 - POST WEEK 52

11 - Harmonisation des code listes… Controlled Terminology

- Reclassements / !!Interprétations
- Implication des équipes +++ / Validation sponsor

CODELISTNAME	RANK	CODEDVALUE	TYPE	sourcedataset	sourcevariable	sourcevalue	sourcetype
REL	1	UNRELATED	CHARACTER	AE_P	AEREL	Unrelated	CHARACTER
REL	2	UNLIKELY RELATED	CHARACTER	AE_P	AEREL	Unlikely	CHARACTER
REL	3	POSSIBLY RELATED	CHARACTER	AE_P	AEREL	Possible	CHARACTER
REL	4	PROBABLY RELATED	CHARACTER	AE_P	AEREL	Probable	CHARACTER
REL	5	RELATED	CHARACTER	AE_P	AEREL	Definitely	CHARACTER

CODELISTNAME	RANK	CODEDVALUE	TYPE	sourcedataset	sourcevariable	sourcevalue	sourcetype
OUT	1	FATAL	CHARACTER	AE_C	AVOUTCOM	Death	CHARACTER
OUT	2	NOT RECOVERED/NOT RESOLVED	CHARACTER	AE_C	AVOUTCOM	Persistent condition	CHARACTER
OUT	3	RECOVERED/RESOLVED	CHARACTER	AE_C	AVOUTCOM	Resolved, no residual effects	CHARACTER
OUT	4	RECOVERED/RESOLVED WITH SEQUELAE	CHARACTER	AE_C	AVOUTCOM	Resolved with sequelae	CHARACTER

12 – SDTM General Considerations – Unique Subject Identifier

- **SDTM General Considerations :**

"The variable USUJID is an identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.
Each individual subject should be assigned a single unique identifier across the entire application.
This is in addition to the subject ID (SUBJID) used to identify subjects in each study and its corresponding study report
An individual subject should have the exact same unique identifier across all datasets, including between SDTM and ADaM datasets.
Subjects that participate in more than one study should maintain the same USUBJID across all studies. It is important to follow this convention to enable pooling of a single subject's data across studies (e.g., a randomized control trial and an extension study)."

- **FDA Guidance:**

"Each individual subject should be assigned a single unique identifier across the entire application. An individual subject should have the exact same unique identifier across all datasets. Subjects that participate in more than one study should maintain the same USUBJID across all studies. It is important to follow this convention to enable pooling of a single subject's data across studies (e.g., a randomized control trial and an extension study)."

- STUDYID = "TOTO" or "TITI"

- TOTO study : USUBJID = TOTO-21-02 → Pool: USUBJID = TOTO-21-02
- TITI study: USUBJID = TITI-21-02 → Pool: USUBJID = TOTO-21-02

13 - Validation de la structure et de la coherence des données

- Pinnacle 21
- Hard coding
- Issues/differences between CDISC and FDA rules
- Recalcul des SEQ
- 1 étude protocolaire + 1 étude d'extension
  - AE en cours de l'étude 1 doivent être reportés en MH dans l'étude 2
  - MH de l'étude 2 doivent être reportés en MH ou AE de l'étude 1
- Structure et contenu d'une base en français
- Détection de doublons dans les AEs des études individuelles
- Issues à documenter dans le cSDRG

Conclusion

- Préserver l'intégrité et l'exactitude des données
- Bien définir les objectifs, le périmètre, la stratégie
- Un travail d'équipe - Implication forte du sponsor indispensable

Modèle unique SDTM

- Choix, arbitrage
- Documentation
- Programmation
- Validation

Ne pas sous-estimer

- L'importance de mobiliser toutes les compétences : biométrie / affaires règlementaires / médical / PV / Rédacteurs médicaux
- Les surprises des études individuelles
- Le temps de mise à jour pour les études en cours

!! Démarrer CDISC le plus tôt possible et pour tous types d'études !!