CDISC v3
The Trial Design Model

Véronique Puyjalon & Nathalie Moro
SANOFI-AVENTIS
Biostatistics & Programming, PHASE I

CDISC French Speakers WG meeting
BAGNEUX, FRANCE
2008 November 17th

sanofi aventis
L'essentiel c'est la santé.

Agenda

- **The Trial Design Model : reminder on concepts**
  - References, Terminology, Definitions
    - Arm, Visit, Element, Inclusion / exclusion
- **Implementation of the Trial Design Model on actual examples**
  - Context of the experience
  - Definition of ARM / EPOCH / ELT variables on 2 different study designs
  - Conclusions : Lessons, Issues and Proposal on EPOCH and TDM
- **Perspectives**

sanofi aventis
L'essentiel c'est la santé.

Concepts of the TRIAL DESIGN MODEL

- **References : STDM version 1.2 ; STDM IG version 3.1.2**
- **TA**
  - **The Trial Arms (TA) dataset describes the sequences of Elements in each Epoch for each Arm, and thus describes the complete sequence of Elements in each Arm.**
  - **TA contain only complete Arm paths, even if a subject drop out of the study before he reach all of the branch points in the Trial design.**
  - **Recommendations to make different schemes before creating TA dataset :**
    - Design scheme
    - Arms scheme
    - Arms and Epochs scheme
    - Blinded View
  - **EPOCH is a required char. variable in the TA defines file.**
  - **A same variable is present in many SDTM (As arm, armcd, visit, visitnum, ..)**

sanofi aventis
L'essentiel c'est la santé.

Concepts of the TRIAL DESIGN MODEL

- **TE**
  - **The Trial Elements (TE) dataset describes the Elements used in the trial.**
  - **TE contains one record for each type of Element in the Trial Arm (TA) dataset, even if an element appear more than one record**
- **TV**
  - **The Trial Visits (TV) dataset describes the planned schedule of visits**
  - **TV contains one record per Planned Trial visit**
- **TI**
  - **The Trial Inclusion / Exclusion (TI) dataset describes the inclusion and exclusion criterias for the trial**
  - **TI contains one record per I/E criterion**
  - **Provided by data management our company**

sanofi aventis
L'essentiel c'est la santé.

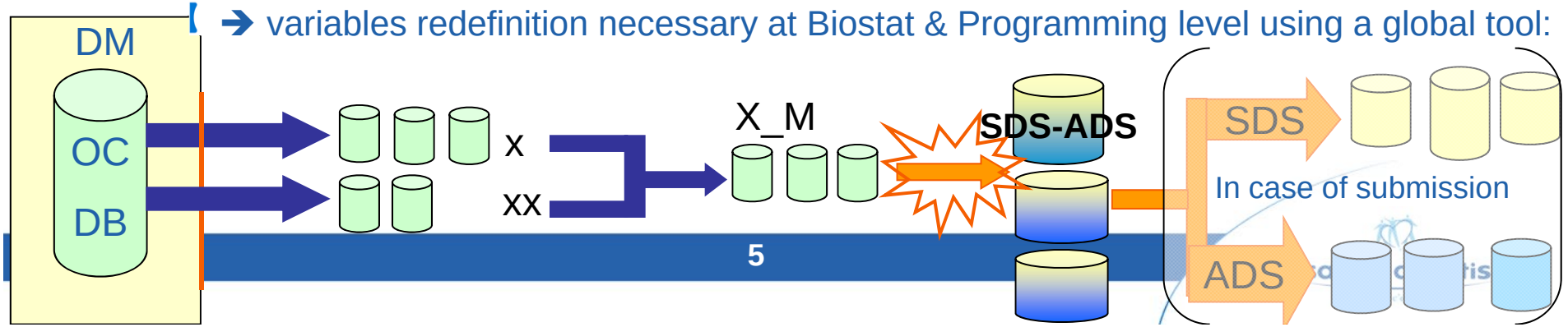
Context of tentative implementation 1/2

Phase I area

- **Many studies with various designs ~100 DBL a year**
- **Definitions must be applicable whatever the design**
  - Strong consistency through designs and time expected (comparison, follow-up etc….) = STABLE STANDARDS necessary
  - Perspective of pool of safety (on 20, 30, 40 Phase I studies)
- **Phase I key step for Clinical development, less important for submission**
  - Except on TES studies (ECG intensive studies) : data sent to FDA

Raw data

- **Views repeated and non repeated retrieved from Oracle Clinical (OC)**
- **A few SDTM variables implemented in the OC views**
- **… some not consistent with SDTM variable definitions = gap between Data Management and Biostat & Programming**
  - ➔ variables redefinition necessary at Biostat & Programming level using a global tool:



Context of tentative implementation 2/2

Scope of experience

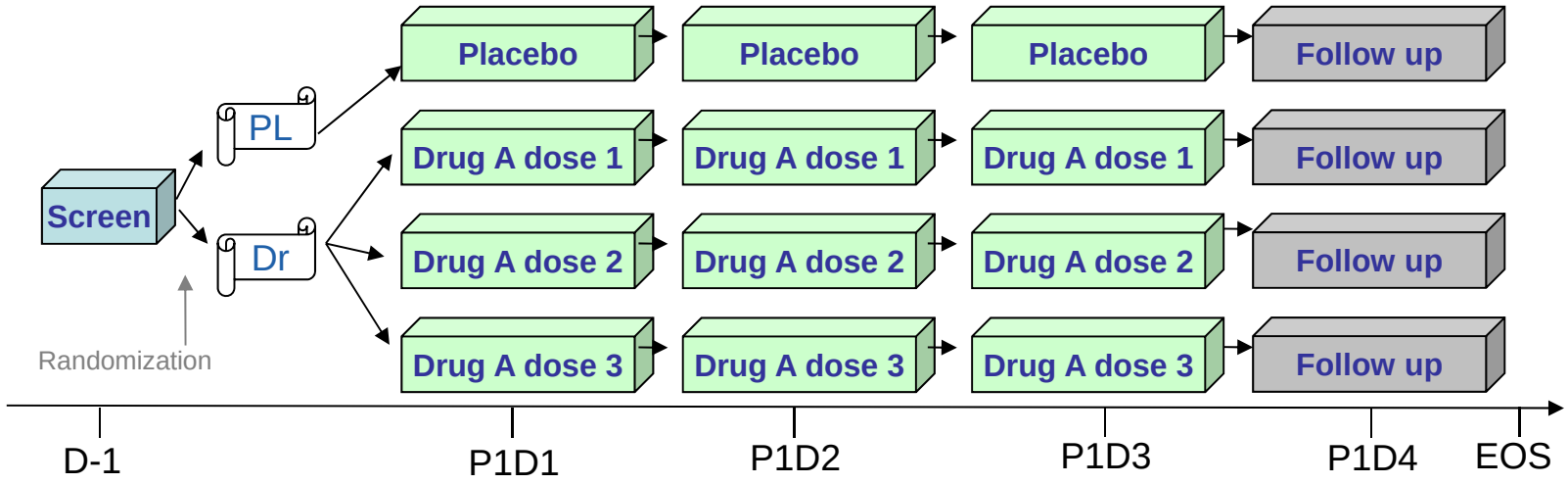
- **CDISC v3 data model for CSR support in Phase I area : a progressive and utility focussed approach**
  - 1 pilot May 2008, 3 others Sept 2008, 2 others Nov 2008 = 6 on 3 different projects in PRODUCTION
  - Some TRIAL DESIGN MODEL variables implemented on ADS in production with adjustements
  - Extend CDISC v3 model in 2009?
- **TRIAL DESIGN tentative implementation on 2 Phase I studies**
  - A parallel design ; A cross-over interaction design
  - Tentative implementation for this presentation

Assessment of utility & criticity regarding analysis perspective

- **ARM & *EPOCH* (?)**
  - Distributed in SDS Disposition
  - Distributed in the ADS (ADEX, ADSV, ADVS…)
  - Critical variables for sort, merge
  - Key variables for statistical analysis and reporting
- **VISIT & IE ➔ Distributed in the other SDS, used in reporting**
- **ELT, BRANCH ➔ specific to Trial Design Model**
  - Not used in any analysis nor reporting

sanofi aventis
L'essentiel c'est la santé.

Example 1 : Parallel design with repeated doses



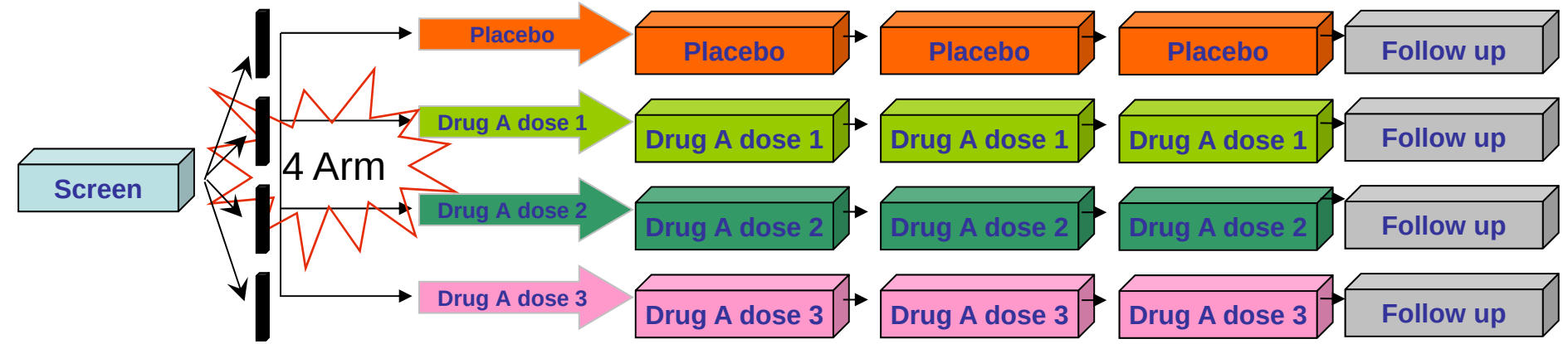
Each cohort does not start at the same time because escalation doses depends on previous one.

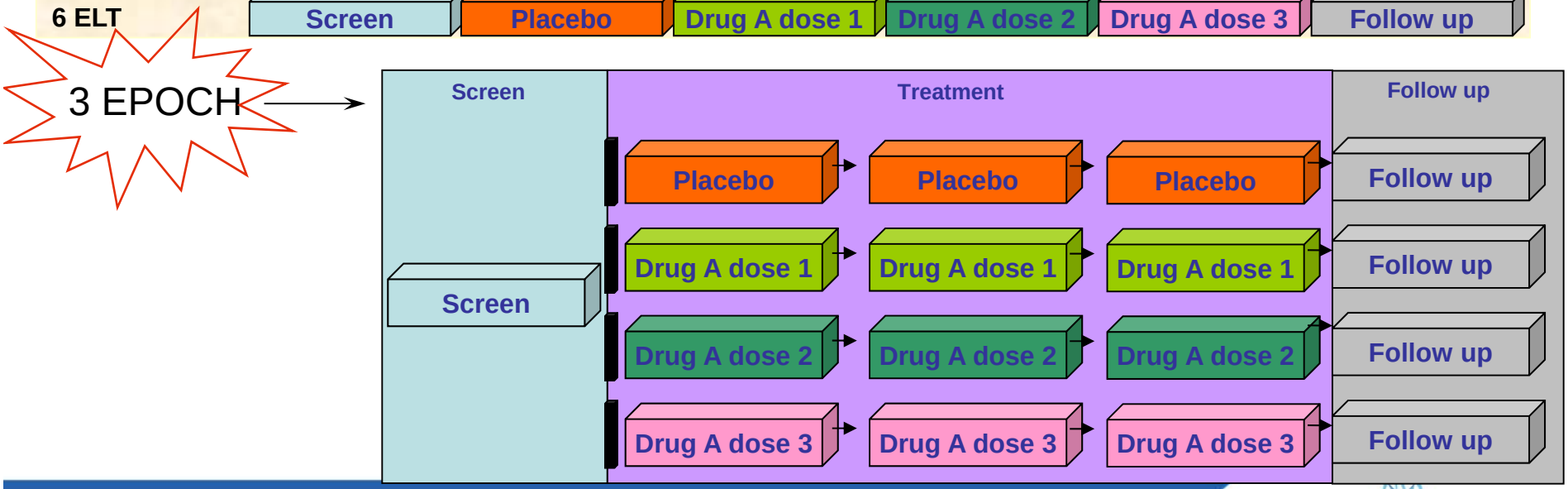
Questions guiding for implementation

- Number and values for ARM?
- Number and values for EPOCH?
- Number and values for ELEMENT?

sanofi aventis
L'essentiel c'est la santé.

Example 1 : ARM, ELT, EPOCH





sanofi aventis
L'essentiel c'est la santé.

Example 1 : TA and TV datasets

Trial Arms (TA) for parallel design :

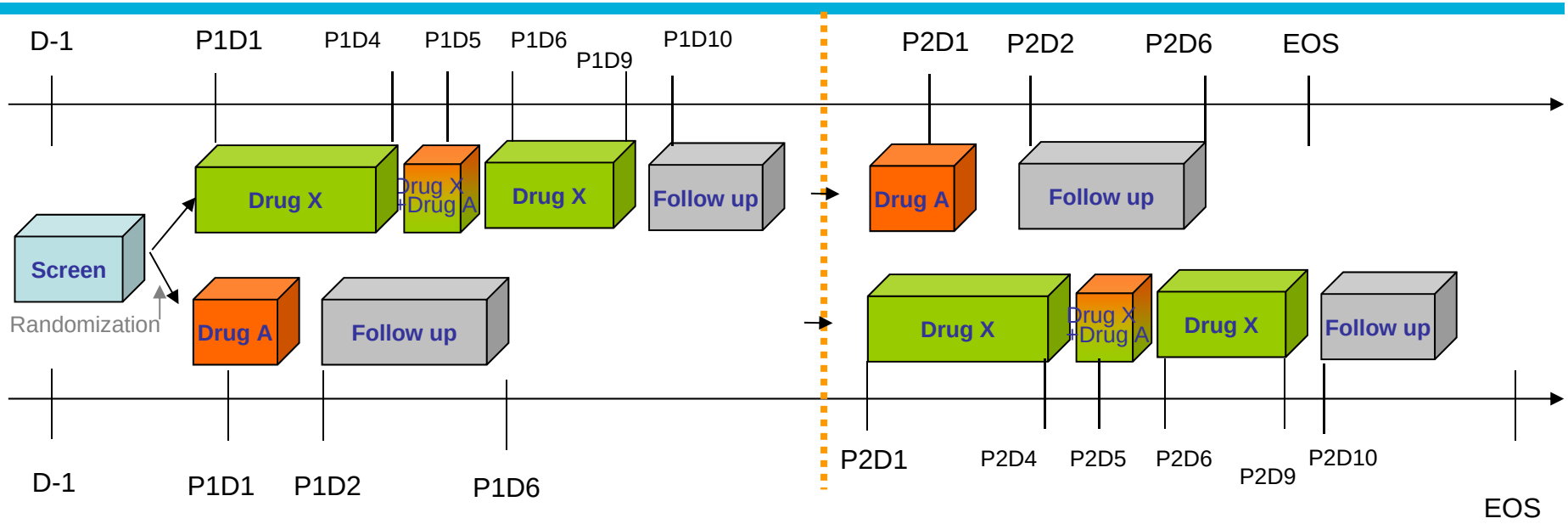
Microsoft Excel Worksheet

Trial Visits (TV) for parallel design :

Microsoft Excel Worksheet

sanofi aventis
L'essentiel c'est la santé.

Example 2 : Cross-over design with co-administration X

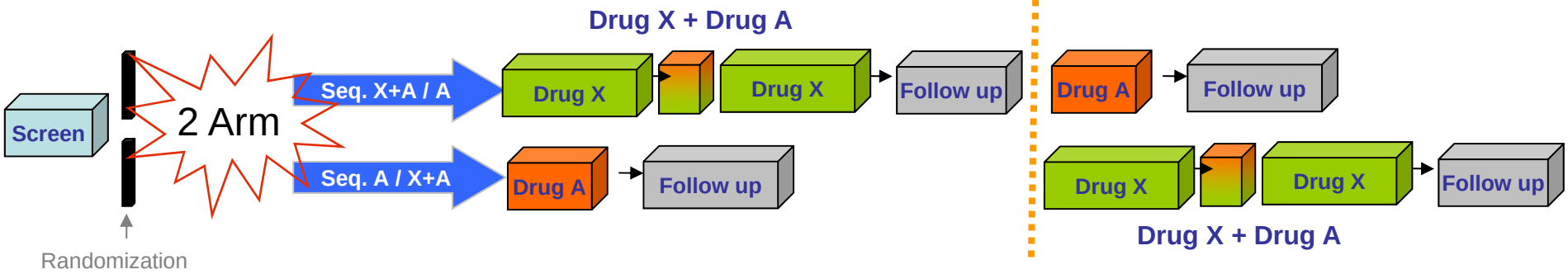


Questions guiding for implementation

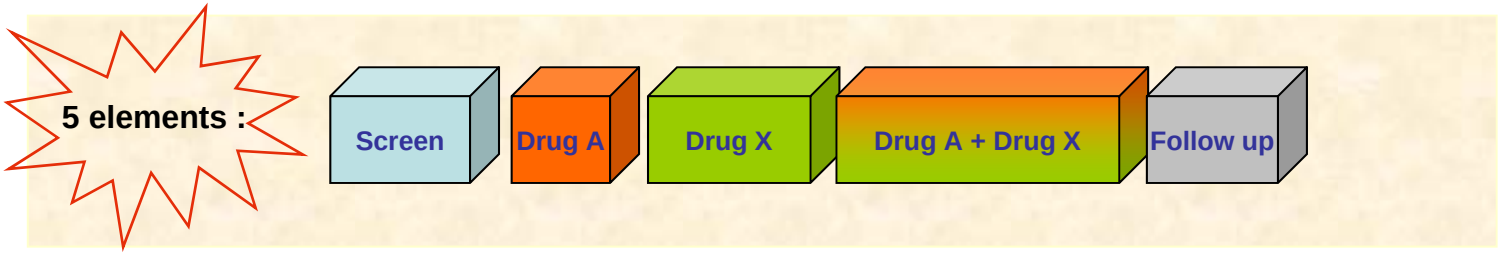
- Number and values for ARM?
- Number and values for EPOCH?
- Number and values for ELEMENT?

sanofi aventis
L'essentiel c'est la santé.

Example 2 : ARM, ELT

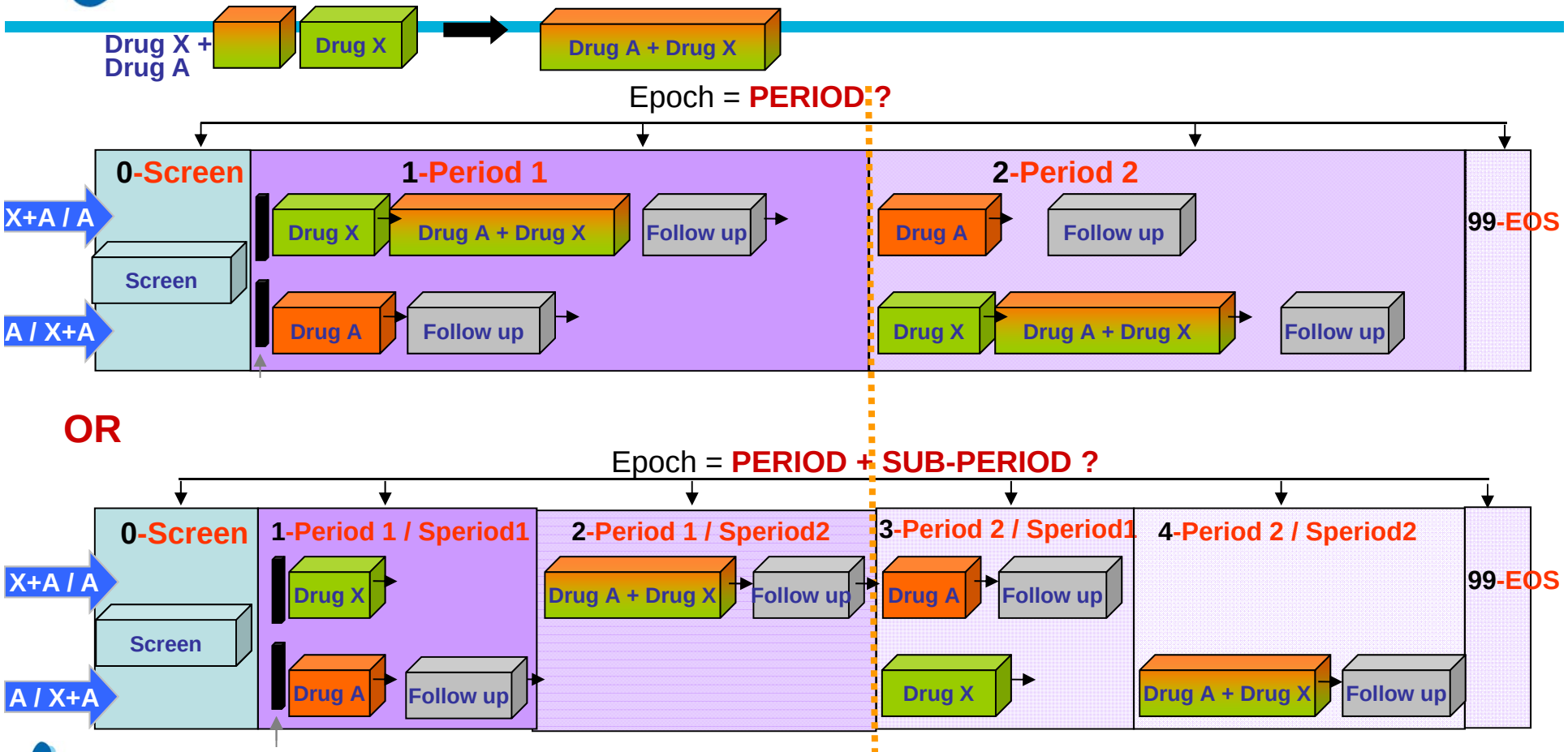


- **ARM : 1 per subject ➔ ARM = randomized sequence of treatments**
  - 2 treatments sequences (used in description of demography)
    - X+A / A
    - A / X+A
- **Treatments for safety & PD analysis (A, X, X+A)**
  - Defined in ADEX, used in ADAE, ADVS, ADEG, ADLB etc…
  - Value X+A must be derived (2 distinct records in raw data)



sanofi aventis
L'essentiel c'est la santé.

Example 2 : some options for EPOCH

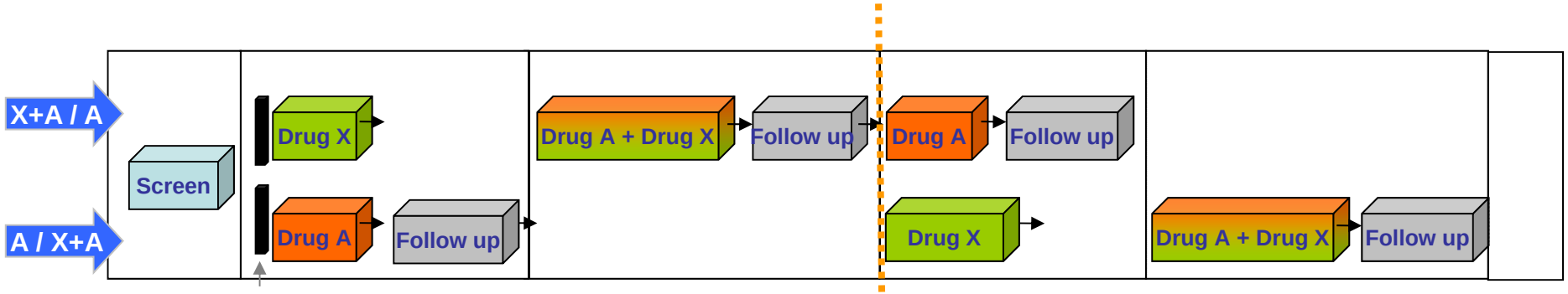


Both approaches are not fully satisfying regarding the need for statistical analysis + risk to misfill EPOCH

- ➔ in agreement with standards responsible, decision to adjust variables in the ADS to cover our critical need, waiting for further directions for a global solution

sanofi aventis
L'essentiel c'est la santé.

Example 2 : the temporary solution for the ADS



PERIOD	Screen	Period 1		Period 2		EOS
PERIODN	0	1		2		99
SPERIOD	Screen	Sub period 1	Sub period 2	Sub period 1	Sub period 2	EOS
SPERIODN	0	1	2	1	2	99

- Combinations of PERIOD & SPERIOD covers the different needs in ADS for data analysis (safety & PD)
- Simple & applicable on all Phase I designs
- Terminology
  - Variables names & labels allow a common understanding across functions in the clinical trial team ('Period' used in ES, protocol, CRF, SAP and CSR)

sanofi aventis
L'essentiel c'est la santé.

Example 2 : Tentative TA and TV datasets

Trial Arms (TA) for cross-over design *(proposal)*:

Microsoft Excel Worksheet

Trial Visits (TV) for cross-over design :

Microsoft Excel Worksheet

sanofi aventis
L'essentiel c'est la santé.

Some lessons on EPOCH variable

- **Expectations / Brief reminders on constraints**
  - **Note on terminology: keep scientific concept of PERIOD**
    - Used from ES to CSR, including in CRF ; critical concept
    - Known by all the functions in Clinical Pharmacology
  - **Period up until +10 for some designs**
  - **PERIOD SPERIOD allow to define study periods with same baseline ➔ change from baseline ➔ safety flag ➔ drug safety assessment**
  - **Homogeneity : Must be applicable on SD dose study as well**
- **Facts on current EPOCH variable**
  - **Definition subject to various interpretations ➔ risk**
  - **Missing variables in the TDM**
    - Period Name
    - Code & name for sub-periods
    - Variables used in current Phase I standards designed for CSR support apart pilots CDISC v3


Microsoft Word Document


Microsoft
werPoint Presentati

sanofi aventis
L'essentiel c'est la santé.

Solutions / Clarifications on EPOCH variable

- **Temporary solution in Sanofi-Aventis in production in Phase I**
  - **in ADS only: PERIOD, PERIODN, SPERIOD, SPERIODN instead of EPOCH**
    - ADSV, ADEX, ADVS, ADEG, ADLB
  - **No TDM produced (no need so far)**
- **Global solution ?**
  - **PERIOD, PERIODN, SPERIOD, SPERIODN instead of EPOCH in ADS and TDM?**
  - **EPOCH = PERIOD, +EPOCHN, SEPOCH, SEPOCHN in ADS & TDM?**
  - **EPOCH = SPERIOD, +EPOCHN, SupraEPOCH, SupraEPOCHN in ADS & TDM?**
  - **EPOCH in TDM / PERIOD, PERIODN, SPERIOD, SPERIODN in ADS?**
  - **Other solutions?**
- **Experience from other companies?**
- **Some recommendations from CDISC?**
- **Feed-back from Phase I pilot studies at the FDA?**
- **Solution to define ASAP globally….**

sanofi aventis
L'essentiel c'est la santé.

Some other comments on TDM

- **Difficult to enter into TDM, questions not resolved by IG, experimentation needed**
  - **Mixed up between different level of pieces of information**
  - **➔ Composite nature SDTM / ADS**

ARM	ELT	VISIT	EPOCH [*PERIOD / SPERIOD*]	IEC
Derivation from CRF data + rando	Derived from ARM	CRF data	From protocol, direct link with the visits	CRF data
Used for reporting	Not used	Used for reporting	Used for reporting	Used for reporting
		Used for analysis	Critical to derive variable for stat analysis	

sanofi aventis
L'essentiel c'est la santé.

Some questions on TDM

- **Why visit information not in TArm?**
- **Why EPOCH not in TVisit? –direct link VISIT - PERIOD**
- **Why EPOCH mandatory in TArm and not in the other SDS?**
- **TDM Positioning?**
  - When creation of TDM?
  - Why definition of TDM is at the end in the guidelines 3.1.2 (section 3 in version 3.1.1)?
- **Clarifications in next CDISC version?**
  - Discussion early 2008 with Diane Wold, GSK & in charge of definition of TDM

sanofi aventis
L'essentiel c'est la santé.

Perspectives

Request from health authorities

- **TDM part of Submission package?**
- **TDM for On-going data communication?**
- **Pool of safety on SDTM : relevant ?**
  - 30, 40 Phase I studies on 15 years of development = various CRFs, standards…

sanofi aventis
L'essentiel c'est la santé.

Questions / Discussion

sanofi aventis
L'essentiel c'est la santé.