CDISC aus der Perspektive der CRO‘s

Herbert Noack

Accovion GmbH, Frankfurt-Eschborn

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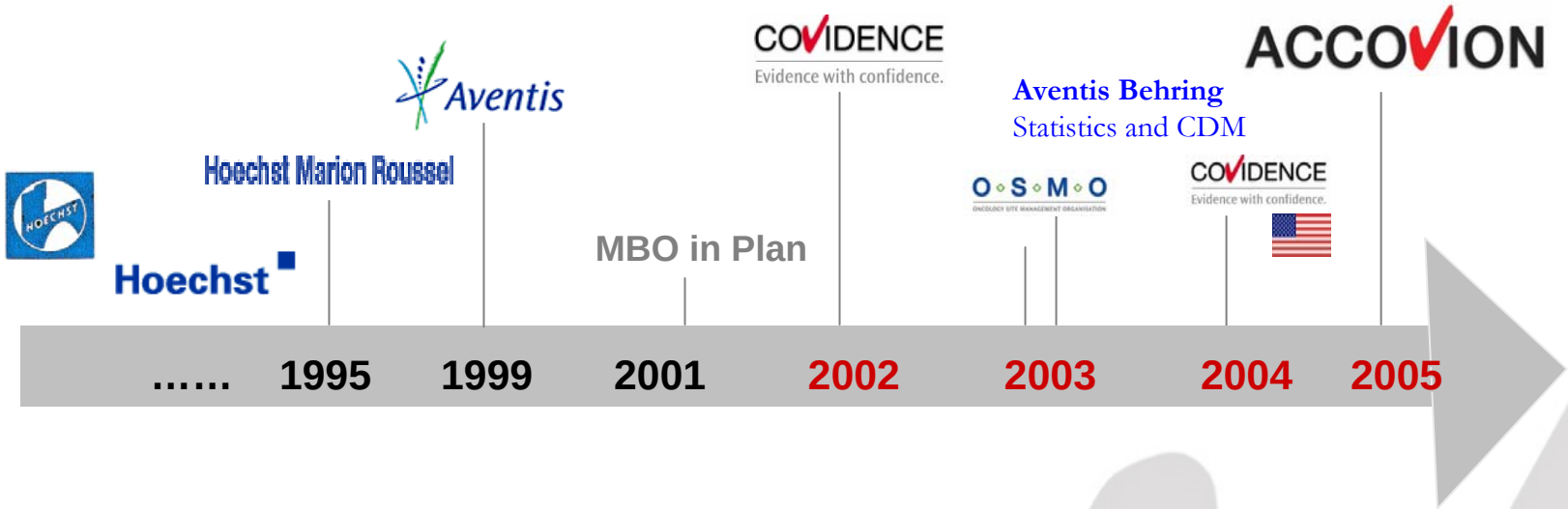
CDISC aus der Perspektive der CRO‘s

Agenda

1. Overview Accovion and CDISC
2. Advantages of CDISC Implementation (Risks?)
3. Implementation SDSv3.1 in CDMS and SAS
4. Indication specific extensions of SDSv3.1
5. Legacy studies

Origins of Accovion

- Accovion is a clinical development service organization formed from the global clinical research, medical writing, pharmacovigilance, biostatistics and data management departments of Aventis (Hoechst) Pharma in Frankfurt.



- Today, more than 200 highly skilled and experienced employees and a network of more than 180 regional study monitors are working on regional and global projects ranging from phase I to IV studies and global submissions.

Therapeutic areas of expertise

Our expertise in all stages of drug development encompasses phase I-IV studies and health outcomes research as well as a significant contribution to a large number of NDAs and MAAs in the following major therapeutic areas:

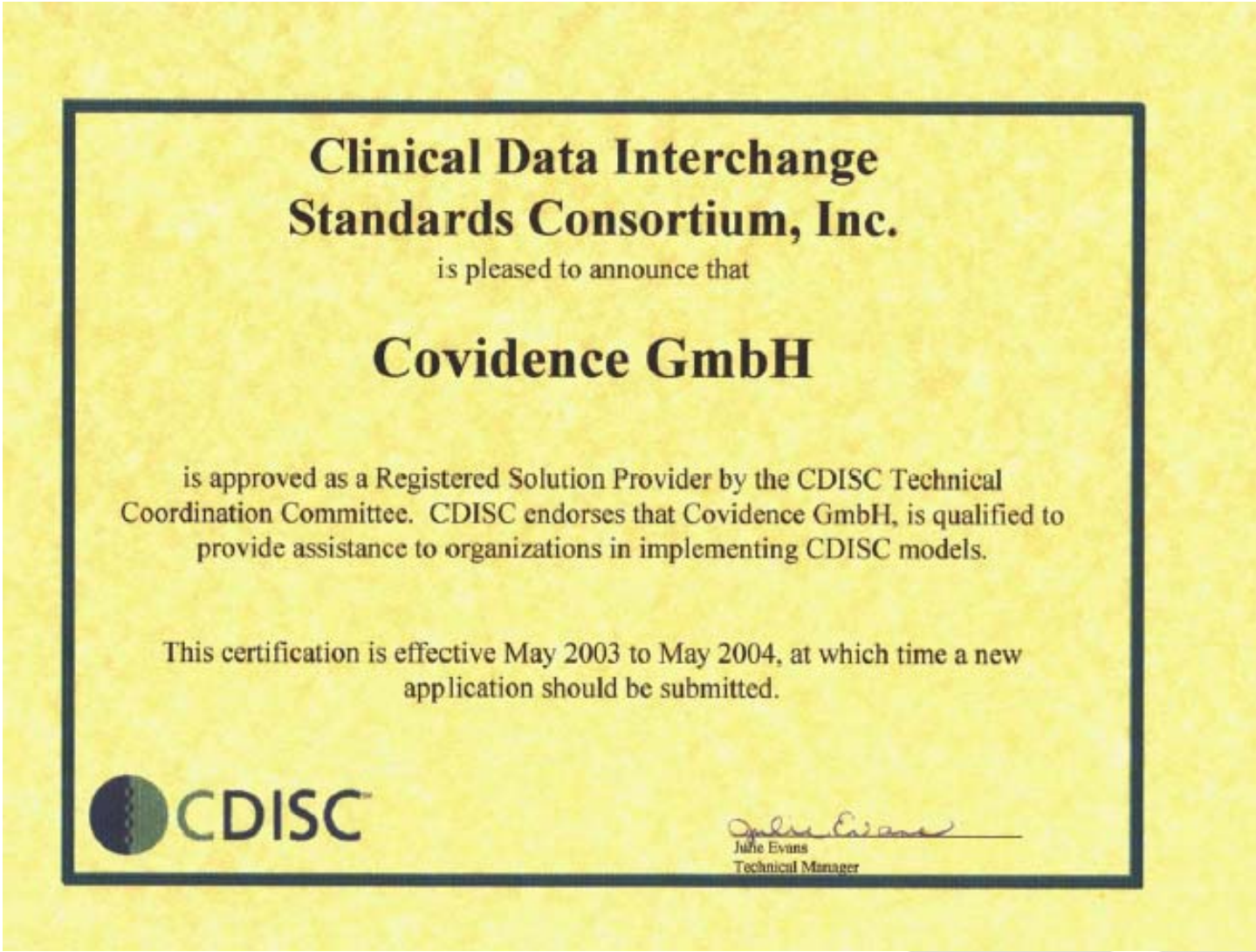
- ✓ Oncology
- ✓ Cardiology
- ✓ Metabolism and Diabetes
- ✓ Inflammation and Rheumatology
- ✓ Immunology
- ✓ Hematology
- ✓ Neurology and Psychiatry
- ✓ Dermatology
- ✓ Allergology
- ✓ Anti-Infectives
- ✓ Plasma Proteins
- ✓ Vaccines
- ✓ Pediatric medicine

Biostatistics, Data Management and Medical IT

With its biostatistics and data management competence centers in **Frankfurt** (Eschborn) and **Marburg**, Accovion is able to provide the full range of services in clinical biostatistics and medical data processing from small first-dose-in-man studies to the largest mega trials:

- ✓ more than 75 users of Clintrial® and Oracle Clinical®
- ✓ 16 database programmers for development and programming of Clintrial and Oracle Clinical databases
- ✓ 19 PhD- or MSc-level statisticians
- ✓ 30 SAS® programmers
- ✓ 12 IT experts specialized in planning, implementation, validation, maintenance and support of IT applications for drug development

‘Registered CDISC Solution Provider’ since May 2003



Clinical Data Interchange Standards Consortium, Inc.

is pleased to announce that

Covidence GmbH

is approved as a Registered Solution Provider by the CDISC Technical Coordination Committee. CDISC endorses that Covidence GmbH, is qualified to provide assistance to organizations in implementing CDISC models.

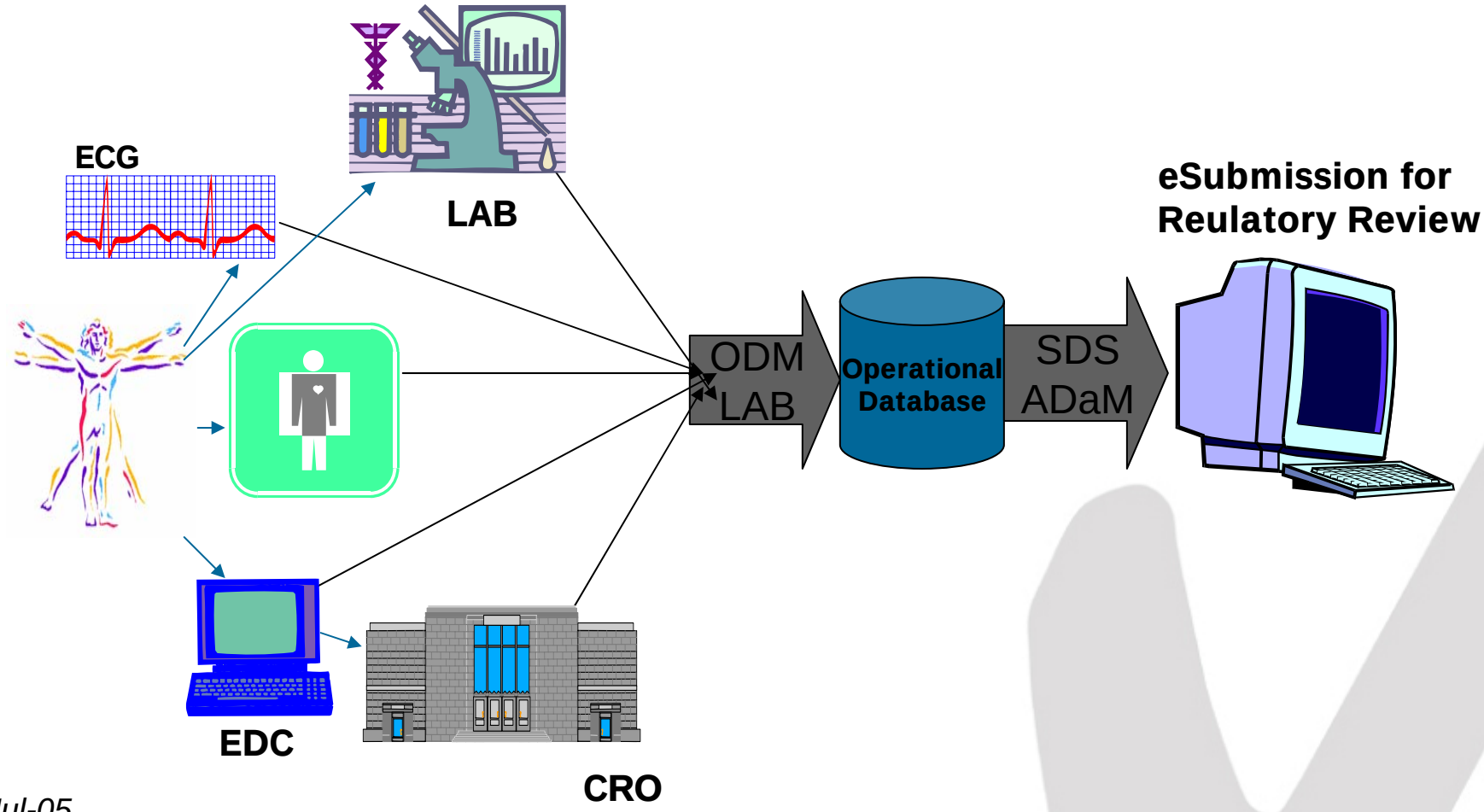
This certification is effective May 2003 to May 2004, at which time a new application should be submitted.

CDISC

Julie Evans
Technical Manager

Data transfer according to CDISC

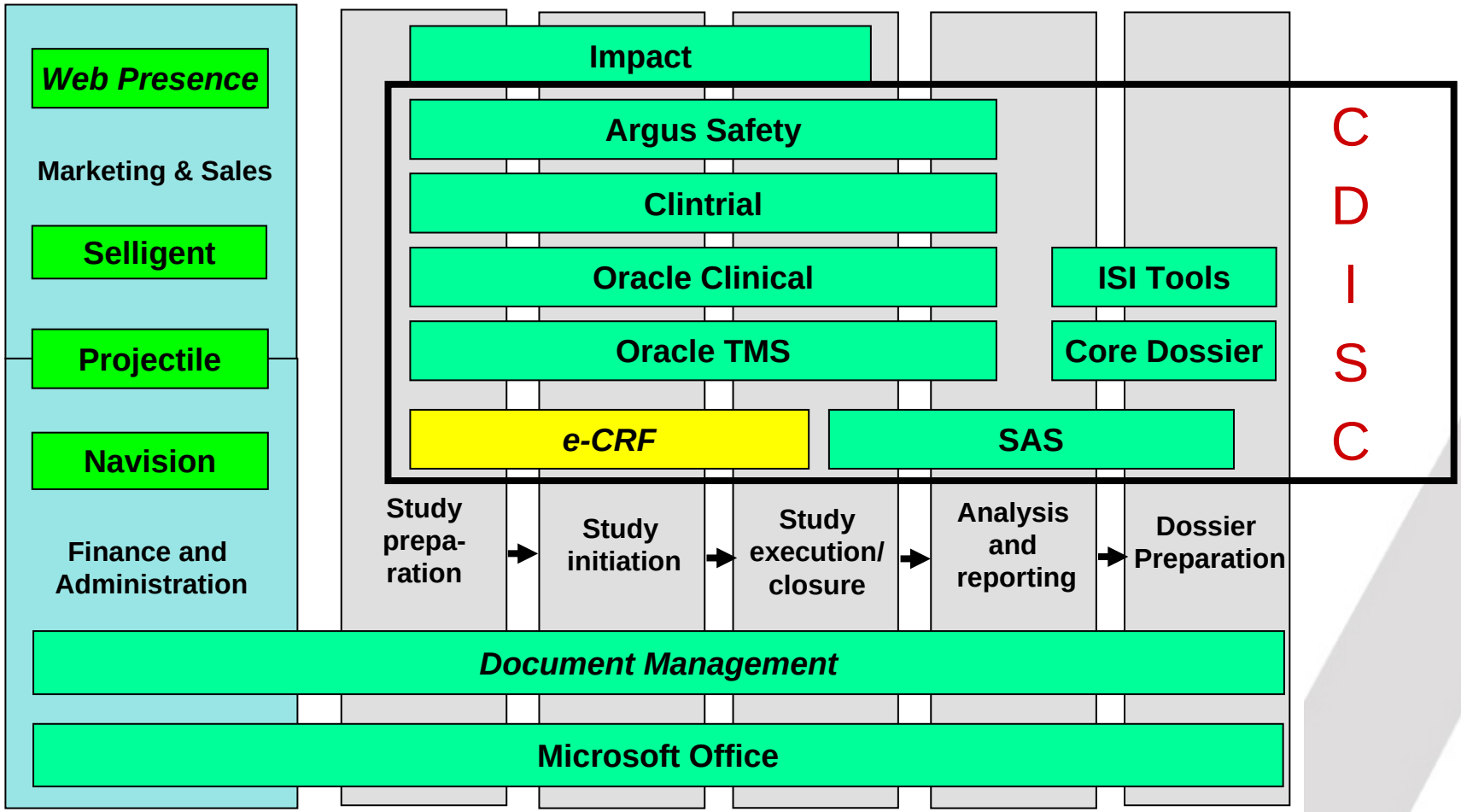
Standards to enable seamless data flow from patiens to reviewers



Reasons for early adoption of CDISC standards at Accovion

- Two painful standardization experiences after mergers
  - Hoechst + MMD => HMR; HMR + RPR => Aventis
  - We were totally convinced by the need for an industry standard
  - Only FDA has the power to set the standard
- We started 2002 with one big customer
  - Other sponsor standards were unkown
- Opportunity to participate in Lab-working group actively
- We have build our CDMS in 2002/2003 based on CDISC-SDSv2
- We expected an earlier recommendation for CDISC-SDS by FDA
  - and a more rapid adoption by industry

Major IT-Applications at Accovion



Importance of SDS for Pharma & CROs

- Advantages:
  - Increased speed and accuracy
    - → Faster trial set-up
    - → Fewer errors in completion, editing & coding
    - → Reduced rework and training
  - Increased efficiency and cost effectiveness
    - → Enhanced visualization if shared understanding of what data are and mean
    - → More clinical research for less money

Additional advantages for CROs

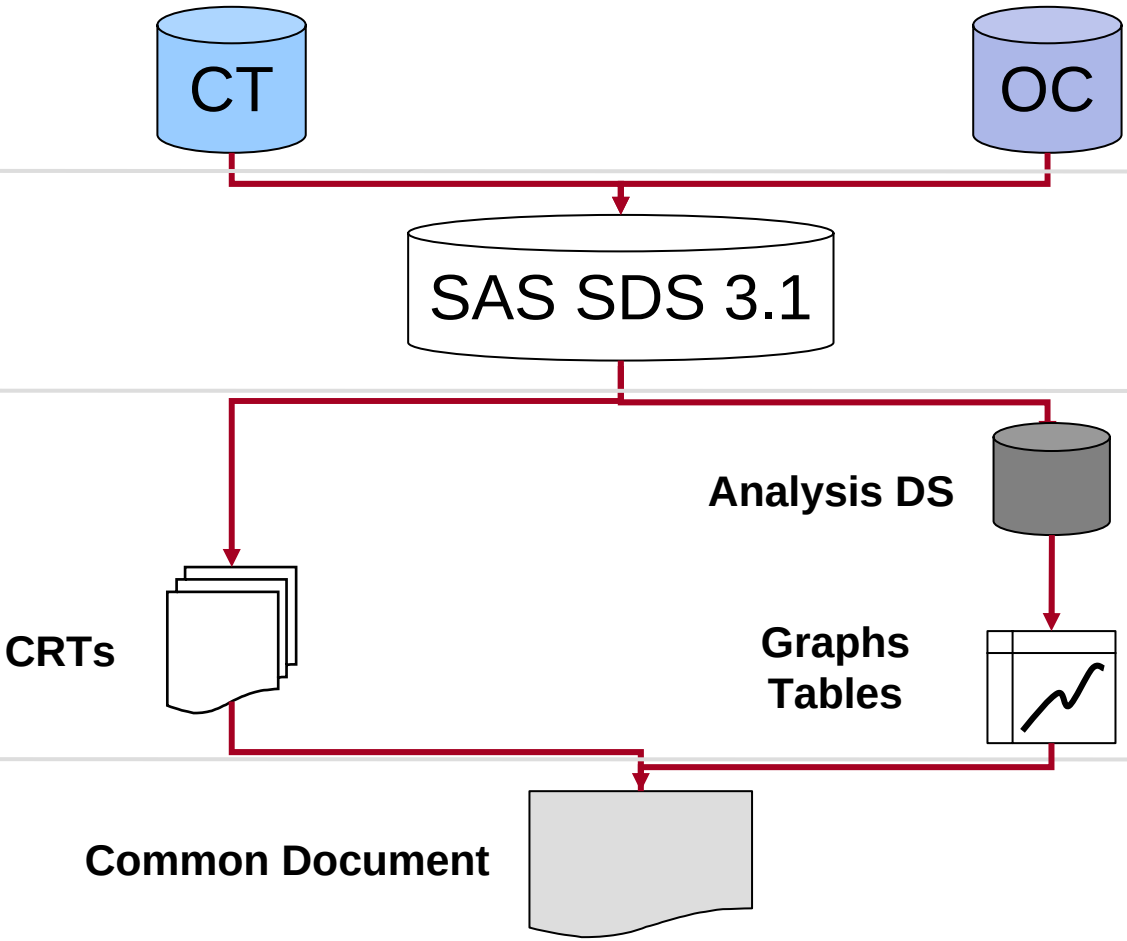
- ✓ Less sponsor specific work required
- ✓ Gain efficancy by standards across sponsors
  - Global data dictionary
  - and sponsor specific extensions
  - Core/standard SAS programs
- ✓ Less e-data source specific work required
- ✓ Increased flexibility of workforce
- ✓ Advantage and Risk:
  Standards lead to a more competitive market

Implementation right from the beginning

Implementation of CDISC Submission Data Standards

- **Start right from the beginning**
  - Create annotated CDISC-SDS CRF-Modules
  - Create CDISC-SDS Data Dictionary in your clinical Database
    - → Add your Codelist (only some standardized, e.g. E2B)
    - → Add project & study specific extensions in SDS logic
  - Add some postprocessing to obtain full SDS compliance in your SAS environment
  - Use SDS files for all CRT tasks
  - Create Analysis Data Files according to ADaM for reporting
  - Create global integrated databases for submission
  - Submit SDS and Analysis Data Files to the FDA

General Data Management/SAS Infrastructure at Accovion



- **Clinical Database**
- **SAS Datasets**
- **Statistical Analysis**
- **FDA Submission**

Design Requirements

- Data dictionary for both, Clintrial and Oracle Clinical
- SAS datasets that are independent of the type of clinical database
- Quality control to ensure conformance to CDISC standard
- Flexibility with sponsor-specific codelist requirements
- Flexibility for sponsor requirements in indication-specific extensions

SDSv3.1 Core domains assigned to Demographics and the three general classes

Demographics – DM
Comment Domain Model – CO

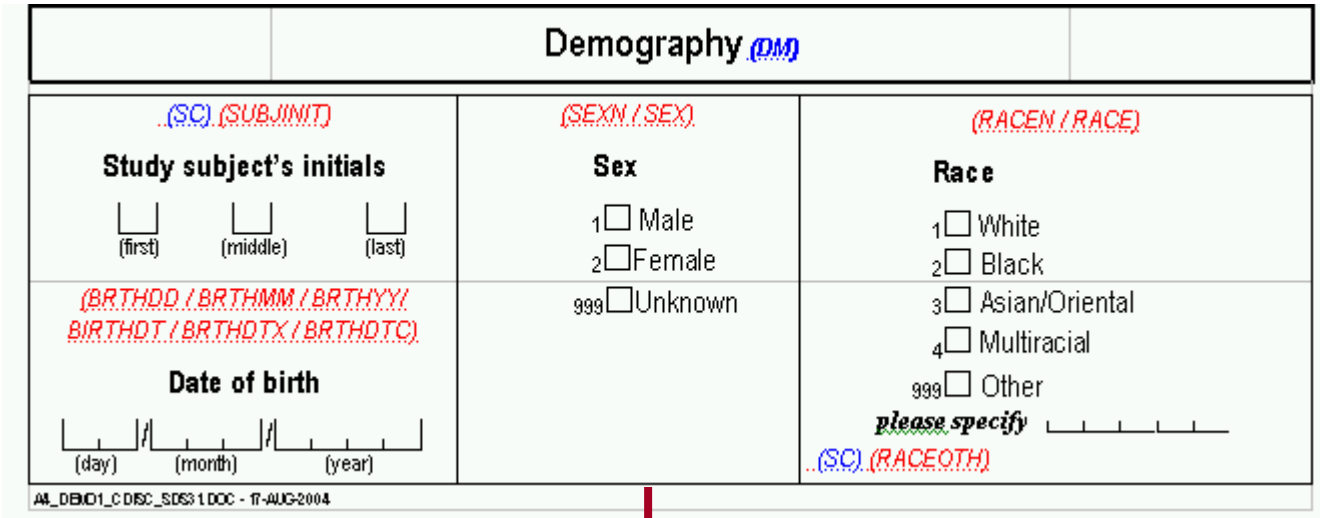
Interventions
- Concomitant Medications - CM
- Exposure - EX

Events
- Adverse Events - AE
- Disposition - DS
- Past Medical History - MH

Findings
- ECG tests - EG
- Inclusion/Exclusion - IE
- Laboratory Tests - LB
- Physical Examinations - PE
- Subject Characteristics - SC
- Substance Use - SU
- Vital Signs - VS

Annotated CRF Module: e.g. DM

CRF



Demography (DM)

(SC) (SUBJINIT)

Study subject's initials

(first) (middle) (last)

(SEXN / SEX)

Sex

1 ☐ Male
2 ☐ Female
999 ☐ Unknown

(RACEN / RACE)

Race

1 ☐ White
2 ☐ Black
3 ☐ Asian/Oriental
4 ☐ Multiracial
999 ☐ Other
please specify
(SC) (RACEOTH)

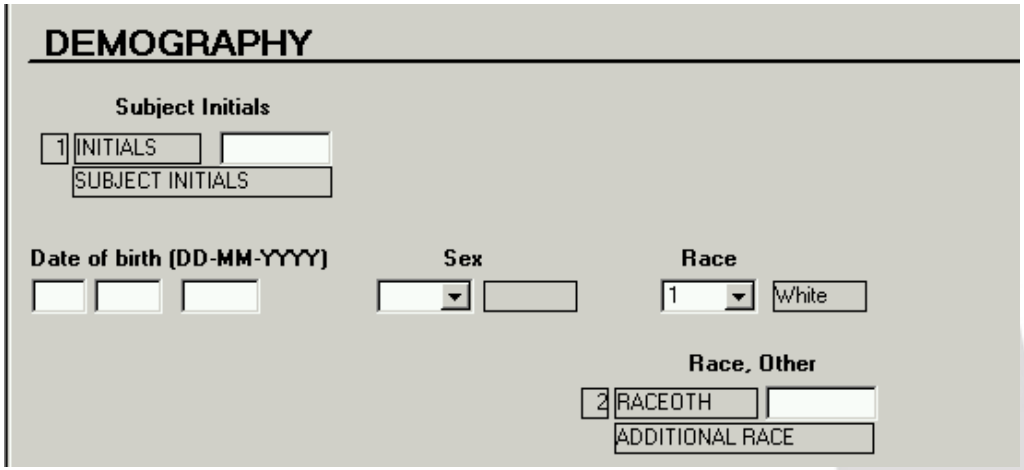
(BRTHDD / BRTHMM / BRTHYY/ BIRTHDT / BRTHDTX / BRTHDTC)

Date of birth

(day) / (month) / (year)

A4_DEMO1_CDISC_SDS3.1.DOC - 17-AUG-2004

Data Entry Screen



DEMOGRAPHY

Subject Initials

1 INITIALS
SUBJECT INITIALS

Date of birth (DD-MM-YYYY)

Sex

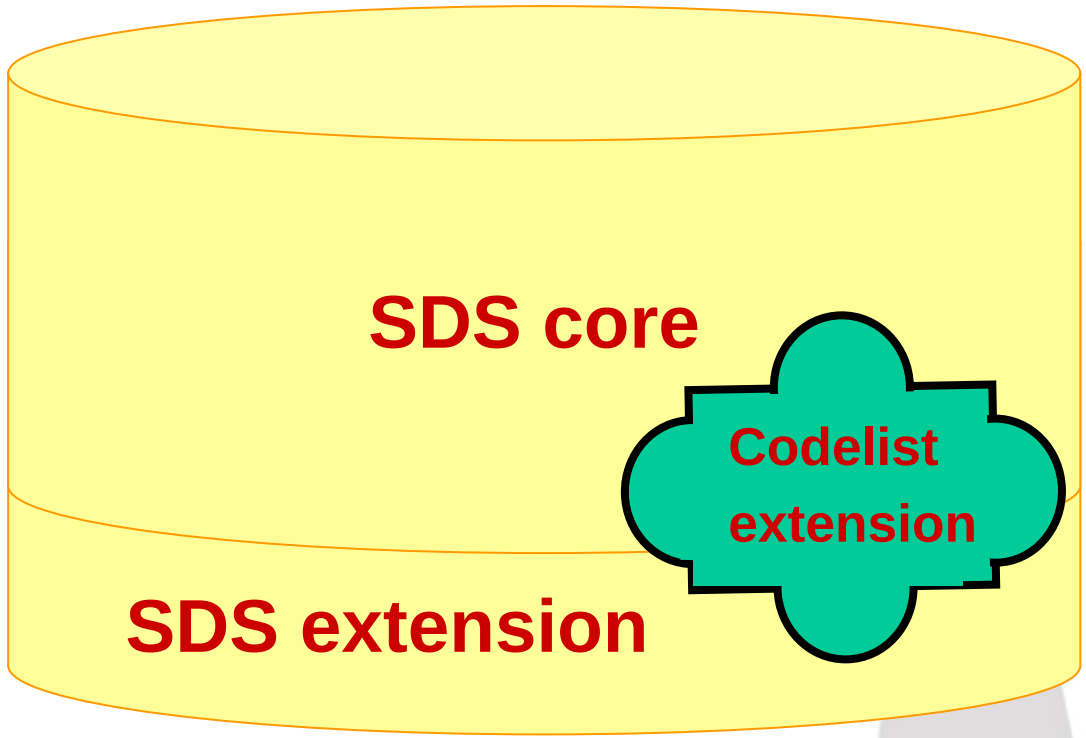
Race

1 White

Race, Other

2 RACEOTH
ADDITIONAL RACE

Implementation of CDISC-SDS study in DBMS

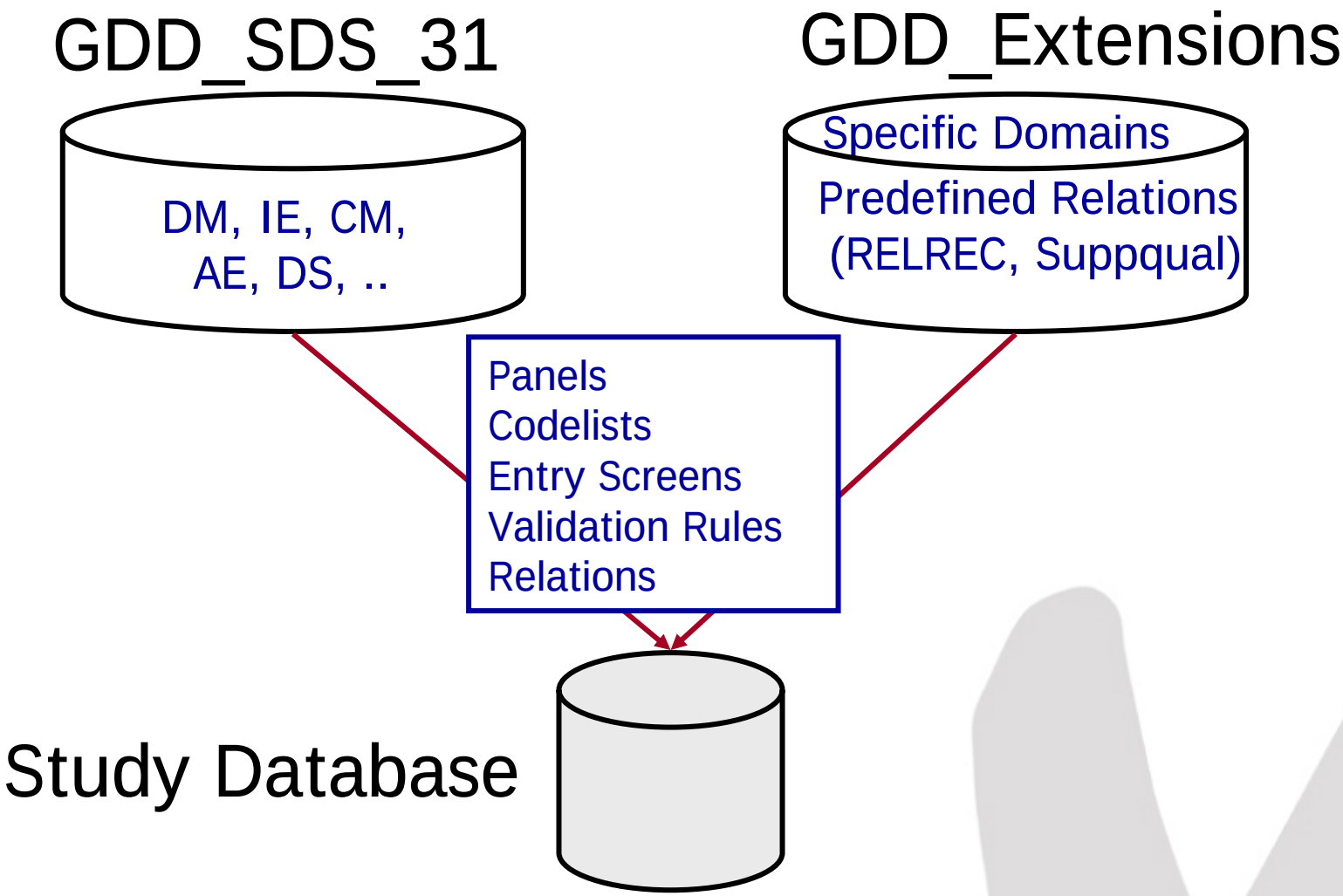


GDD Structure for Standard Domains

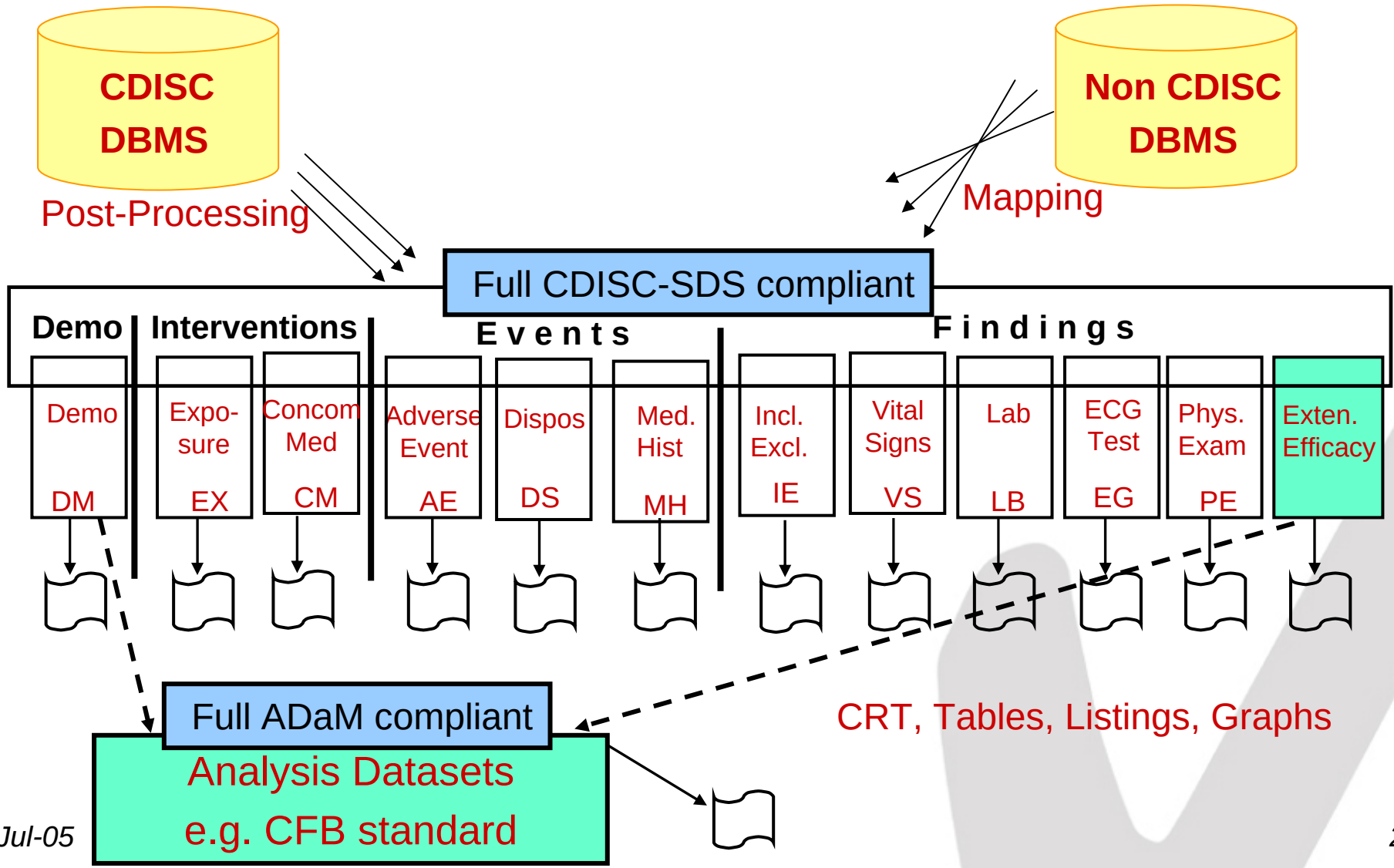
Protocol	Panel	Type	Installed	Tables	Marked	Vld Proc	Description
GDD_SDS_31	AE	>1 Record per Patient Visit	☑	☑	☐	Valid	Events - Adverse Events
GDD_SDS_31	CM	>1 Record per Patient Visit	☑	☑	☐	Valid	Interventions - Concomitant Medications
GDD_SDS_31	CO	>1 Record per Patient Visit	☑	☑	☐	Valid	Comments
GDD_SDS_31	CONTEXT	>1 Record per Patient Visit	☑	☐	☐	None	Context
GDD_SDS_31	DM	1 Record per Patient	☑	☑	☐	Valid	Demographics
GDD_SDS_31	DS	1 Record per Patient	☑	☑	☐	Valid	Events - Disposition
GDD_SDS_31	EG	>1 Record per Patient Visit	☑	☑	☐	Valid	Findings - ECG
GDD_SDS_31	ENROLL	Subject Enrollment	☑	☑	☐	Valid	Enrollment Panel
GDD_SDS_31	EX	>1 Record per Patient Visit	☑	☑	☐	Valid	Interventions - Exposure
GDD_SDS_31	IE	>1 Record per Patient Visit	☑	☑	☐	Valid	Inclusion / Exclusion Exceptions
GDD_SDS_31	LB	>1 Record per Patient Visit	☑	☑	☐	Valid	Findings - Labs
GDD_SDS_31	MH	>1 Record per Patient Visit	☑	☑	☐	Valid	Events - Medical History
GDD_SDS_31	PE	>1 Record per Patient Visit	☑	☑	☐	Valid	Findings - Physical Exam
GDD_SDS_31	QS	>1 Record per Patient Visit	☑	☑	☐	Valid	Findings - Questionaires
GDD_SDS_31	RELREC	>1 Record per Patient Visit	☑	☑	☐	Valid	Relations
GDD_SDS_31	SC	>1 Record per Patient	☑	☑	☐	Valid	Findings - Subject Characteristics
GDD_SDS_31	SU	>1 Record per Patient Visit	☑	☑	☐	Valid	Interventions - Substance Use
GDD_SDS_31	SUPPQUAL	>1 Record per Patient Visit	☑	☑	☐	Valid	Supplimental Qualifiers
GDD_SDS_31	VS	>1 Record per Patient Visit	☑	☑	☐	Valid	Findings - Vital Signs

- All SDS 3.1 variables for standard domains
- Sponsor-defined codelists
- Database-specific items

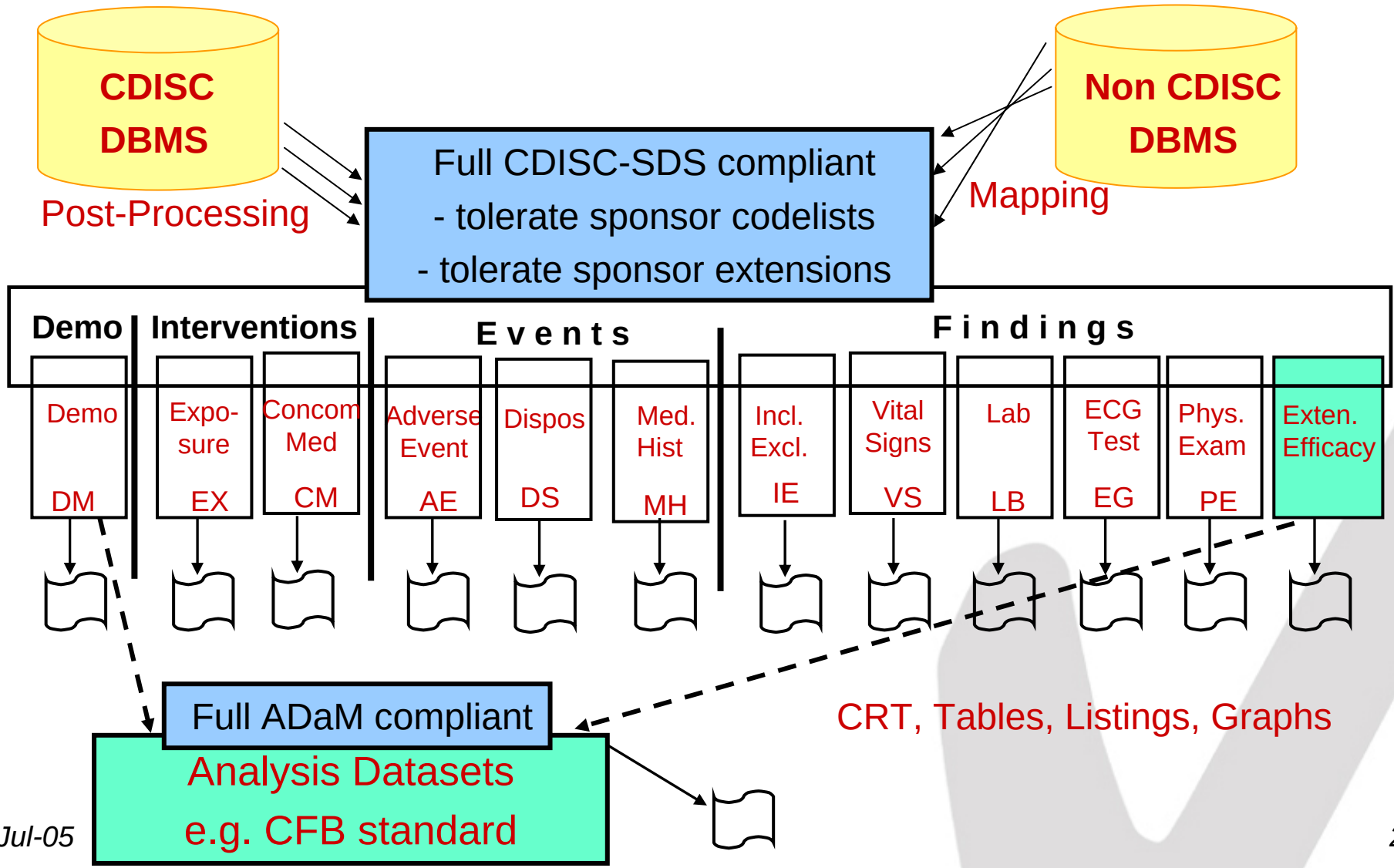
Creation of a study database



Implementation of CDISC-SDS in SAS



CRO: Implementation of CDISC-SDS in SAS



Implementation at Accovion

- Standard tables for study reports / submissions -

- Study Table Shells (to be prepared by Biostatistician)
  - List of tables
  - Copy of needed Core tables
    specify: column headers, column width, presentations of missings, etc.
  - Create new tables if not available within Core Tables
- List of tables:
  - Preliminary numbering
  - Title
  - Underlying Population (one table for each population)
  - Variables to be used
  - Core Table Number

Implementation at Accovion - Core Tables

- Document Core Tables:
  - Description of Contents
  - Layout of Standard Tables
  - Options (Totals, p-values, presentation of percentages etc.)
  - Definition of underlying datasets
- SAS Macro available for each Core Table:
  - Input: SAS dataset with formatted treatment groups
    e.g. Placebo, Drug A 1 mg, Drug A 5 mg, Total Drug A
  - Macro calculates specified descriptive statistics
  - Prepares Output file (to be defined: .lst, .rtf, .html)

Implementation at Accovion

- Standard Core Tables Directory (example) -

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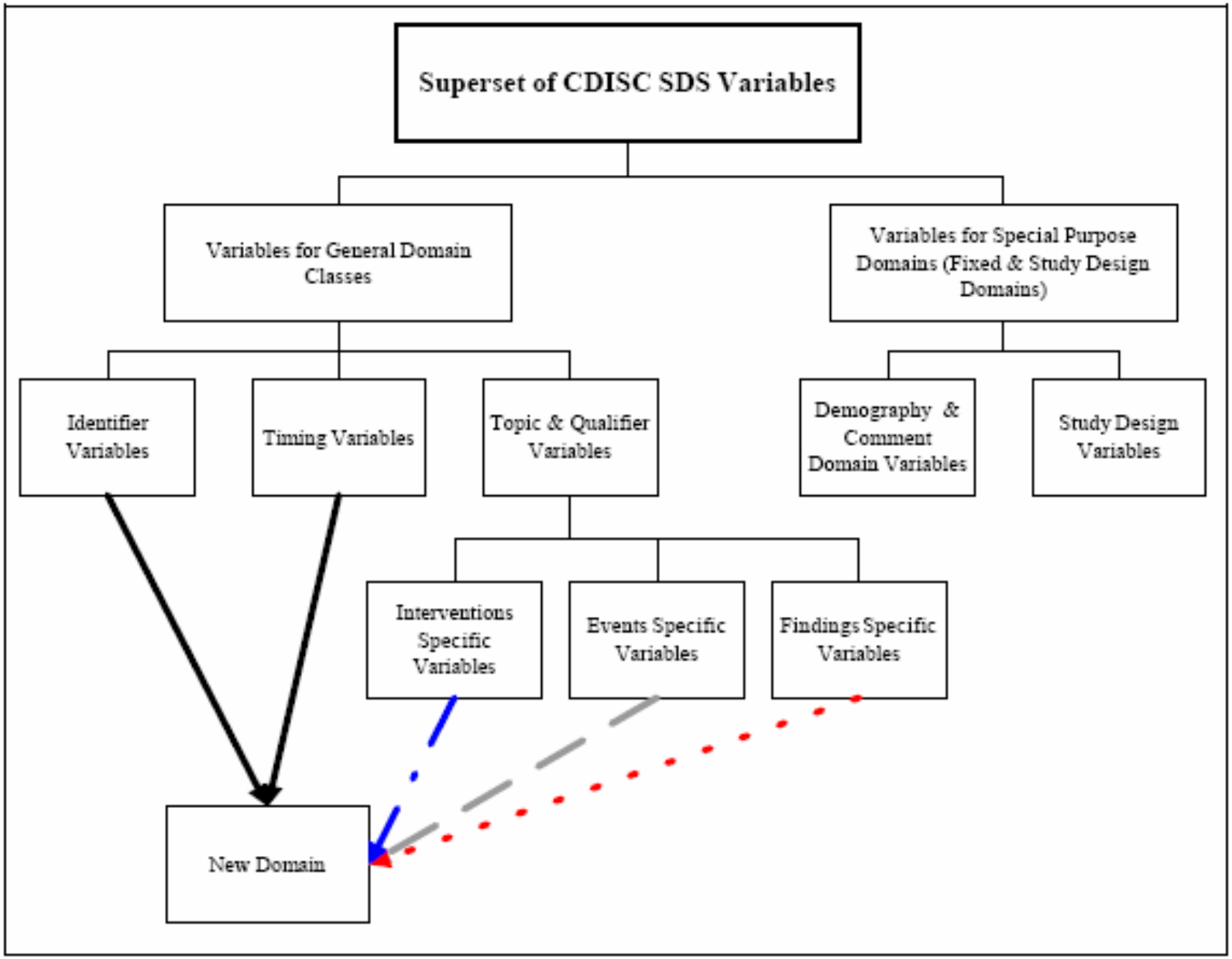
Indication specific extensions of SDSv3.1

SDSV3.1 Strategy for new domains

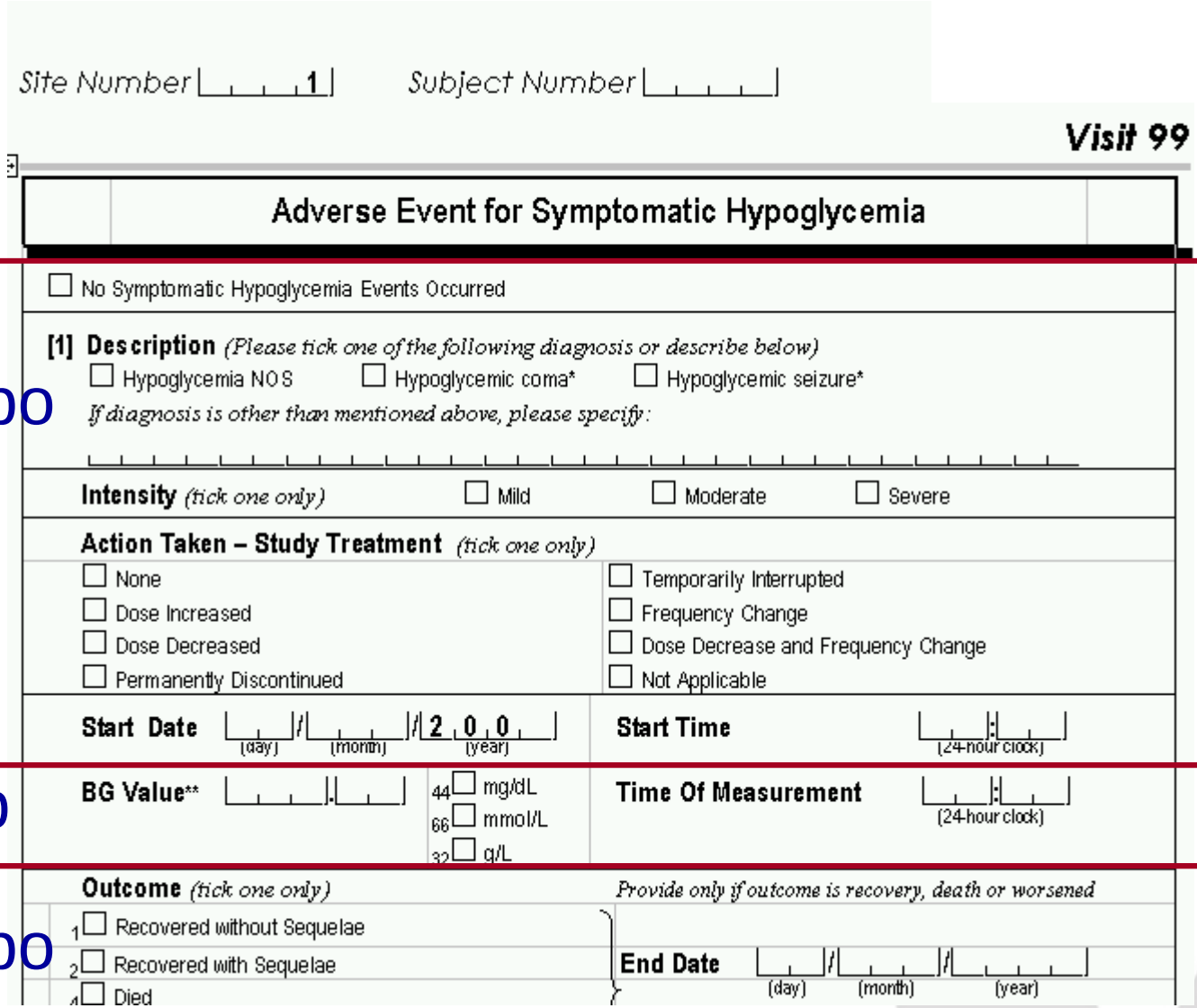


Extension example: Diabetology

- Common safety/efficacy data: Hypoglycemic Events (Hypos)
- Similar to Adverse Events
- Importance of data justify separate domain
- Overall data fit into Event Model

New Domain: HG

Hypo CRF



Site Number 1 Subject Number

Visit 99

Adverse Event for Symptomatic Hypoglycemia

☐ No Symptomatic Hypoglycemia Events Occurred

[1] Description *(Please tick one of the following diagnosis or describe below)*

☐ Hypoglycemia NOS ☐ Hypoglycemic coma* ☐ Hypoglycemic seizure*

If diagnosis is other than mentioned above, please specify:

Intensity *(tick one only)* ☐ Mild ☐ Moderate ☐ Severe

Action Taken – Study Treatment *(tick one only)*

☐ None
☐ Dose Increased
☐ Dose Decreased
☐ Permanently Discontinued
☐ Temporarily Interrupted
☐ Frequency Change
☐ Dose Decrease and Frequency Change
☐ Not Applicable

Start Date (day)/(month)/2 0 0 (year) **Start Time** (24-hour clock)

BG Value** 44 ☐ mg/dL 66 ☐ mmol/L 32 ☐ g/L **Time Of Measurement** (24-hour clock)

Outcome *(tick one only)* *Provide only if outcome is recovery, death or worsened*

1 ☐ Recovered without Sequelae
2 ☐ Recovered with Sequelae
☐ Died

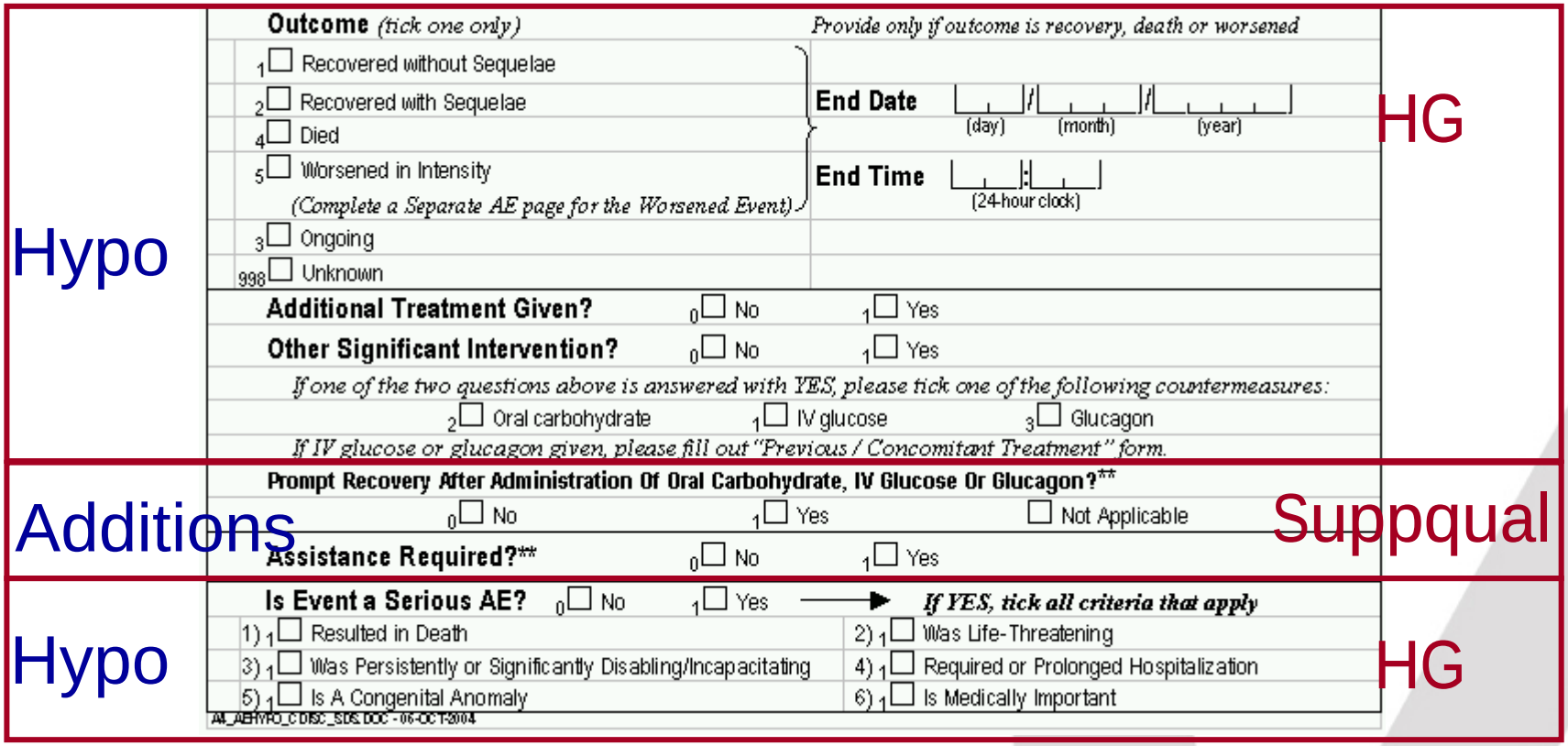
End Date (day)/(month)/(year)

Hypo — HG

Lab — LB

Hypo — HG

Hypo CRF (lower part)



Outcome *(tick one only)*

Provide only if outcome is recovery, death or worsened

1 ☐ Recovered without Sequelae
2 ☐ Recovered with Sequelae
4 ☐ Died
5 ☐ Worsened in Intensity
(Complete a Separate AE page for the Worsened Event)
3 ☐ Ongoing
998 ☐ Unknown

End Date ___/___/_____ (day) (month) (year)

End Time ___:___ (24-hour clock)

Additional Treatment Given? 0 ☐ No 1 ☐ Yes

Other Significant Intervention? 0 ☐ No 1 ☐ Yes

If one of the two questions above is answered with YES, please tick one of the following countermeasures:

2 ☐ Oral carbohydrate 1 ☐ IV glucose 3 ☐ Glucagon

If IV glucose or glucagon given, please fill out "Previous / Concomitant Treatment" form.

Prompt Recovery After Administration Of Oral Carbohydrate, IV Glucose Or Glucagon?**

0 ☐ No 1 ☐ Yes ☐ Not Applicable

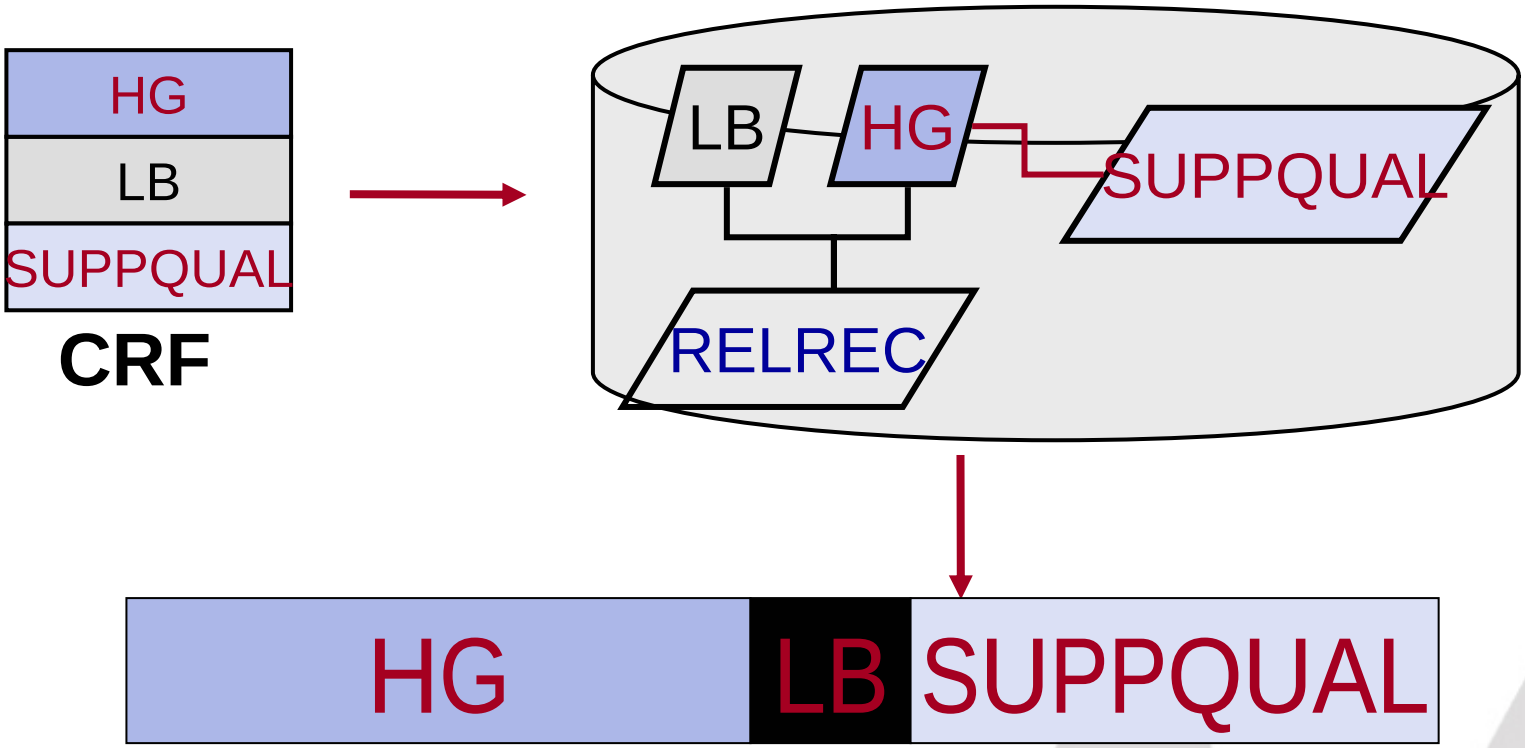
Assistance Required?** 0 ☐ No 1 ☐ Yes

Is Event a Serious AE? 0 ☐ No 1 ☐ Yes → ***If YES, tick all criteria that apply***

1) 1 ☐ Resulted in Death
2) 1 ☐ Was Life-Threatening
3) 1 ☐ Was Persistently or Significantly Disabling/Incapacitating
4) 1 ☐ Required or Prolonged Hospitalization
5) 1 ☐ Is A Congenital Anomaly
6) 1 ☐ Is Medically Important

AE_AEHYPO_C DISC_SDS.DOC - 06-OCT-2004

Analysis Datasets for Hypo



Legacy studies, what to do?

Recommendations for legacy projects

Project status	CDMS	SAS Environ-ment	SAS analysis progs	Recommendation
Before sub-mission	Non-CDISC	Non-CDISC	Non-CDISC	Map integrated SAS-DB to SDS and ADaM; rerun each study report using ADaM datasets for validation
Last Phase III study, reporting started	Non-CDISC	Non-CDISC		Map into SDS, develop analysis datasets from SDS according to ADaM; develop integrated SAS-DB according to SDS and ADaM and rerun each study report using ADaM datasets for validation
Phase III running	Non-CDISC			Map into SDS, develop analysis datasets from SDS according to ADaM; prepare integrated SAS-DB of phase II studies according to SDS and ADaM and rerun each study report using ADaM datasets for validation