# The Implementation of ICH Development Safety Update Report (DSUR) Guidance

**PhUSE SDE Switzerland**
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**Angelo Tinazzi**
**Cytel Inc., Wilmington Del. USA**
**Succursale de Meyrin – Geneva – Switzerland**
**angelo.tinazzi@cytel.com**

# Agenda

- **Background and Overview of the new ICH Guidance**
- **Implications for study sponsors**
  - **Detailed process**
  - **Timeline**
  - **The Clinical Trials Inventory**
  - **Data-Management**
- **Implementation in Biostatistics Department**
  - **Data Mapping Approaches**
  - **Type of Outputs to be provided**
- **Conclusions**

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  - Type of Outputs to be provided
  - Use of CDISC principles
- Conclusions

# Background and Overview of the new ICH Guidance

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- Regular analysis of safety is crucial for the assessment of risk to trial subjects and to understand the risk-benefit of a medical product
- PSUR (Periodic Safety Update Report) is for post-marketing periodic reporting
- For medical product under development (IMP), some ICH countries required submission of periodic safety report
  - Differences in the content
  - Differences in the format
  - Differences in the timing

(1) US IND Annual Report [21 CFR 312.33]

(2) EU Annual Safety Report [2001/20/EC and ENTR/CT3]

(3) Japan Investigational Product Serious / Infection Case Priodical Report' – 6 monthly [PFSB 0229011 Feb 08 and 1001005 Oct 08]

# Background and Overview of the new ICH Guidance

## Overview and Benefits of new DSUR ICH Guidance - DSUR History

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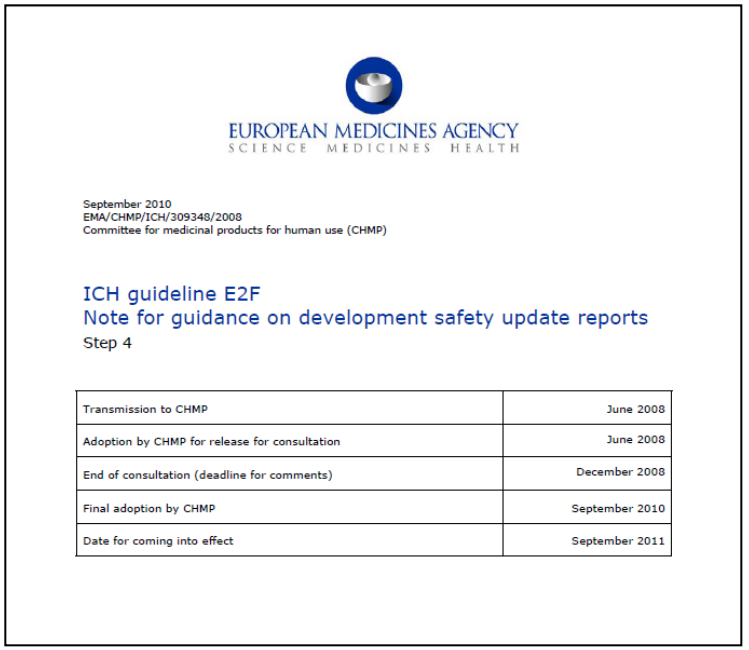
ICH guideline E2F – Note for guidance on development safety update report:

September 2010: Final adoption by CHMP

September 2011: Date for coming into effect

August 2011: FDA Guidance to industry document

http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm073109.pdf



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

September 2010
EMA/CHMP/ICH/309348/2008
Committee for medicinal products for human use (CHMP)

ICH guideline E2F
Note for guidance on development safety update reports
Step 4

| | |
|---|---|
| Transmission to CHMP | June 2008 |
| Adoption by CHMP for release for consultation | June 2008 |
| End of consultation (deadline for comments) | December 2008 |
| Final adoption by CHMP | September 2010 |
| Date for coming into effect | September 2011 |

ICH E2F DSUR

EMA/CHMP/ICH/309348/2008

E2F Development Safety Update Reporrt FDA Aug 2011

# Background and Overview of the new ICH Guidance

## Overview and Benefits of new DSUR ICH Guidance

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The DSUR is an annual review and evaluation of pertinent safety information related to an Investigational Medical Product, before and after marketing authorization

- Safety information during the **current review period**
- Analysis of new information based on previous knowledge of the product safety
- Consistent regulatory terminology
- Co-ordinated **periodicity** of reports
- Same **scope** and **content** for same trials in different regions

# Background and Overview of the new ICH Guidance

## Overview of new DSUR ICH Guidance – Key points

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| | |
|---|---|
| **DIBD**<br>Development International Birth Date | The sponsor's first authorization to conduct a clinical trial in any country worldwide. It is used to determine the start of the annual period for DSUR |
| **DLP**<br>Data Lock Point | The last day of the one-year reporting period |
| Scope | Molecule |
| Periodicity | Once a year no more than 60 calendar days from DLP |
| Information to be included | Any completed and ongoing trials:<br>•All Indications<br>•All strenghts<br>•All formulations<br>•All patients populations |
| PSUR Overlap | PSUR and DSUR both needed when Clinical Trials continue after market approval |

# Background and Overview of the new ICH Guidance

## Overview of new DSUR ICH Guidance – By-Period vs Cumulative Outputs


*By-Period Outputs*

Only ‘events’ occurred in the reporting period (one year)


*Cumulative Outputs*

All ‘events’ occurred since DIBD up to DLP

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# Implications for study sponsors
## Before DSUR

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- Multiple reports (e.g. one for FDA one for EMA)
  - Multiple database cleaning / extract
  - Multiple outputs programming tasks
- Unclear requirements for outputs production
- Last minute requests
- No central coordination (e.g. from safety dept)

# Implications for study sponsors
## Detailed Process

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- Develop cross-functional SOPs / Process Guide
- **Track** of projects requiring DSUR
  - Development International Birth Date (**DIBD**)
  - Countries / Regions requiring submission
  - Identification of Trials to be included
    - **Clinical Trials Inventory**
- Outputs
  - Grouping of studies
  - Identification of Additional outputs/rules to be provided / followed
- Outputs from SAE database
- Standard mapping rules / outputs programs

# Implications for study sponsors

## The Clinical Trial Inventory

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- **All «interventional» studies ph 1 to 4** sponsored by «sponsor XXX»
  - No observational studies
  - Corporate and non-corporate from all regions
  - Non corporate trials can be incorporated but usually provided by Medical Affairs
  - Planned vs Ongoing vs Completed study
    - **Planned**
    - **Ongoing**

      when the study was approved by any Health Authorities in or before the review period
    - **Completed**

      ICH-E2F: defined as “a trial for which a final CTR is available, so locked db and there is no further collection of data
  - **Stratification factors** (indication, formulation, etc.)
  - Key Contacts (CRO, DM, Trial Manager)

# Implications for study sponsors
## Data Management

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- Retrieving/Extracting data for multiple studies
  - **In-house / CRO / Investigator Trials**
  - Other trials when the medical product is used in combination to other IMP(s)
- Data cleaning/reconciliation as much as possible
  - Demography, Adverse Events, Exposure, Disposition, Deaths
  - SAE reconciliation
- MedDRA version alignment not needed
  - Complete coding not needed

# Implications for study sponsors

## Possible Timeline

**List of CTRs**

**DSUR author specify grouping / additional outputs / blinding**

Additional info from literature search

Individual Case Safety Report

**DIBD DLP**

**Db Extract**

**Safety and Stat Outputs**

Additional inputs and reviews

**DSUR Submission**

**-1Yr** -60d -35d -15d -1d **0** +2d +7d +32d **+60d**

*Reporting Period*

24JAN2012 23JAN2013

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# Implementation in Biostatistics Department

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- Clear **process** definition e.g. SOP
- **Technical Guidance**
  - Global Derivation Rules
  - Standard Mapping
  - Outputs Templates including SAS Program Templates
- **Aligning differences in existing SAPs**
  - Definition of Treatment Emergent AEs
  - Definition of Population e.g. Safety vs ITT Population
- Blinding
- Application of **data cut-off** / **reporting period**
- Identification of new information from previous reporting period
  - **Maintaining historical data** (e.g. DSUR2012, DSUR2013, etc)

# Implementation in Biostatistics Department

## Data Mapping Approaches

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### Option 1


- Available in late stage projects when for example submission effort already occurred
- Harmonization already occurred
- Trial domains facilitate identification / reporting of trial characteristics

# Implementation in Biostatistics Department

## Data Mapping Approaches

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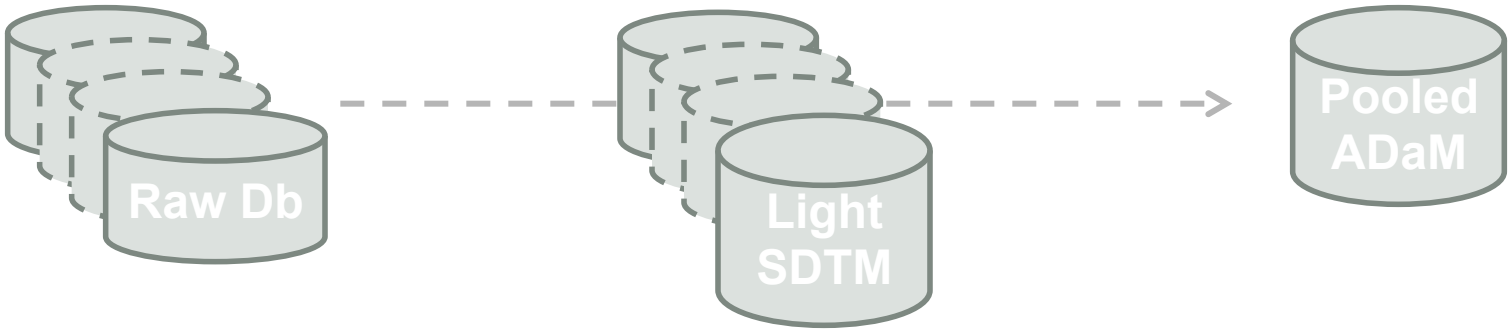
### Option 2




- The most common situation of early stage development projects or projects where CDISC investment did not yet occur
- Light SDTM can be the start of the CDISC «effort»
  - TS (Trial Summary Datasets)
  - DM (Demographics), AE (Adverse Events), EX (Exposure), DS-light (light disposition) for deaths / end of treatment

# Implementation in Biostatistics Department

## Data Mapping Approaches

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### Option 3


- The most common situation of early stage development projects or projects where CDISC investment did not yet occur
- Harmonisation effort directly in the pooled ADaM including Controlled Terminology

# Implementation in Biostatistics Department

## Data Mapping Approaches - ADaM Pooling - ASDL

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ADSL For the purpouse of DSUR:

- Demographics
- Arms/Treatments Grouping
- Study Population
- Trial Indication and additional stratification factors
- Deaths and Disposition

In addition

- Compliance / Exposure (Subject Years)

# Implementation in Biostatistics Department

## Data Mapping Approaches - ADaM Pooling - ADAE

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ADAE For the purpouse of DSUR:

- Description including coding terms (PT and SOC)
- Action Taken, Outcome, SAE, Severity
- Drug (IMP) relationship
- Treatment Emergent Identification
  - Imputation of partial start date as per company standard
  - AE started before first IMP administration and within xx days from last IMP drug administration (follow-up period). E.g. 50 days
- Flag of **events belonging to the reference period**

# Implementation in Biostatistics Department

## Data Mapping Approaches - ADaM Pooling

## Standard Corporate ADaM requirements for DSUR - Additional Rules

- Exposure (Subject-years)= sum for all subjects of

  [(min(last treatment admin date, end of reporting period) – first treatment admin date) +1] / 365.25

- Compliance derivation depends on indication/type of therapy

  e.g. relative dose-intensity in oncology

# Implementation in Biostatistics Department

## Type of Outputs to be Provided

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| Outputs to be provided from clinical trials database as an appendix | |
|---|---|
| 3a. Status of Ongoing and completed trials | Cumulative |
| 3b. Estimated cumulative exposure | Cumulative |
| 4a. Cumulative subject exposure to IMP by age and gender | Cumulative |
| 4b. Cumulative subject exposure to IMP by racial group | Cumulative |
| R2a. Tabulation of ongoing trials with number of subject drop out count | Cumulative |
| R2b. List of subject who died during the reporting period | Period |
| R2c. List of subject dropped out during the reporting period due to AE | Period |
| R3. Cumulative tabulation of AEs with frequency higher than 5% | Cumulative |
| SAE. Cumulative summary tabulation of serious adverse events | Cumulative |
| Compliance. Subject compliance to study drug in the reporting period | Period |

Rxx, are applicable to US only
The numeration above is the numeration choosen by one of our customer
**Study is always used as a 'stratification' factor**

# Implementation in Biostatistics Department

## Type of Outputs to be Provided

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## Depending on the status of the IMP development

- Additional Stratifications
  - By Indication
  - By Dosage
  - Type of drug used in combination.
    - E.g. drugs containing a specific agent
- Additional Outputs
  - Pooled adverse events tables
  - SMQ and other AEs of «potential» interest

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Examples / Templates

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The table can be automatically created if SDTM is available (e.g from trial domain)

β.a : Status of Clinical Studies
Table 3.a.2 : Completed Studies

| Study Identifier | Ph. | Country | Title | Dosing Regimen | Population | Subjects Exposed |
|---|---|---|---|---|---|---|
| 013 | I | France<br>Germany | Open-Label, Randomized, Controlled Phase I Study Of _ To Evaluate The | | Subjects With Recurrent/Metastatic Squamous Cell Cancer Of The Head Or Neck | 2wk 00mg : 3<br>2wk 000mg : 3<br>2wk 000mg : 4 |

Output ID: T_3a 0

| | STUDYID | DOMAIN | TSPARMCD | TSPARM | TSVAL |
|---|---|---|---|---|---|
| 1 | 013 | TS | ADDON | Added on to Existing Treatments | Y |
| 4 | 013 | TS | AGESPAN | Age Group | ADULT (>18) |
| 5 | 013 | TS | AGEU | Age Unit | YEARS |
| 8 | 013 | TS | DOSE | Dose per Administration | 500 or 2000 |
| 9 | 013 | TS | DOSFRQ | Dosing Frequency | QD for 4 days then QS or BIS |
| 10 | 013 | TS | DOSU | Dose Units | mg |
| 11 | 013 | TS | INDIC | Trial Indication | RECURRENT/METASTATIC SQUAMOUS CELL CANCER OF THE HEAD AND NECK |
| 12 | 013 | TS | OBJPRIM | Trial Primary Objective | Phase II part: To assess the progression-free survival (PFS) in subjects with recurrent an... |
| 18 | 013 | TS | PLANSUB | Planned Number of Subjects | 177 |
| 19 | 013 | TS | RANDOM | Trial is Randomized | Y |
| 20 | 013 | TS | RANDRAT | Ratio for Randomization | 1:1:1 |
| 24 | 013 | TS | SPONSOR | Clinical Study Sponsor | I |
| 25 | 013 | TS | TBLIND | Trial Blinding Schema | OPEN LABEL |
| 26 | 013 | TS | TCNTRL | Control Type | COMPARATIVE TREATMENTS |
| 27 | 013 | TS | TDIGRP | Diagnosis Group | SUBJECTS WITH RECURRENT/METASTATIC SQUAMOUS CELL CANCER OF THE... |
| 28 | 013 | TS | TINDTP | Trial Indication Type | TREATMENT |
| 29 | 013 | TS | TITLE | Trial Title | Open-label, randomized, controlled Phase I/II study of cilengitide to evaluate the safety ... |
| 30 | 013 | TS | TITLE | Trial Title | in subjects with recurrent/metastatic squamous cell cancer of the head and neck (ADV... |

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Examples / Templates

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**Table 3b: Estimated Cumulative Subject Exposure from Ongoing and Completed Clinical Trials**
**Safety Population**

| Study Identifier | Investigational arm Number of subjects | Sum of Subject-Years |
|---|---|---|
| [illegible]_3062 | 18 | 53.60 |
| [illegible]- 02 | 80 | 3.03 |
| [illegible] 003 | 33 | 5.94 |
| [illegible]-004 | 53 | 4.68 |
| [illegible]-005 | 53 | 5.10 |
| [illegible]-006 | 16 | 9.15 |
| [illegible]-010 | 4 | 0.21 |
| Overall | 419 | 101.71 |

Safety_Monitoring\Safety_Report\Pooled\DSUR_2012\Primary\TLF\Pgm\Tables\Appx3b.sas 03DEC2012
Cut off date = 23NOV2012.
Subject Year = (Last Exposition Date to - First Exposition Date to + 1) / 365.25.
Output ID: Appx3b 03DEC2012 20:41

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Examples / Templates

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Table 3.b : Cumulative Subject Exposure in Ongoing and Completed Trials by Indication

| Exposure To: | Healthy Subjects N(subject -yrs) | Subjects With ---------- N(subject -yrs) | Subjects With SCCHN N(subject -yrs) | Subjects With NSCLC N(subject -yrs) | Total N(subject -yrs) |
|---|---|---|---|---|---|
| Monotherapy | 104 ( 5.0 ) | 81 ( 36.1 ) | 130 ( 55.0 ) | 105 ( 17.1 ) | 395 ( 67.9 ) |
| Combination Therapy | 15 ( 0.2 ) | 497 (439.1 ) | | 7 ( 58.7 ) | 833 (572.1 ) |
| Any Therapy | 119 ( 5.2 ) | 578 ( 5.2 ) | 130 ( 55.0 ) | 2_2 ( 75.7 ) | 1 28 (63 .9 ) |
| Comparator Therapies | | 343 (172.6 ) | 62 ( 34.5 ) | 112 ( 36.2 ) | 559 (257.1 ) |
| Total | 119 ( 5.2 ) | 92 (647.8 ) | ( 89.5 ) | 54 (111.9 ) | 1787 (897.0 ) |

Data cut-off date: June 2013.
Subjects are reported as treated.
(a) Subjects included into study 001 as well as into study 002 are counted twice.

Example from a late stage development program with stratification by **indication** and **type of combination therapy**

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Examples / Templates

## Example of Treatments Grouping in ADSL

| TRT01PN | TRT01P |
|---|---|
| 1 | IMP 500 MG |
| 2 | IMP 1000 MG |
| 3 | IMP 1500 MG |
| 4 | IMP 1000 + TREATMENT WITH XX |
| 5 | IMP 1500 + TREATMENT WITH YY |
| 6 | IMP 2000 + TREATMENT WITH XX |

} Derived from ARMCD

Use of standard ADaM ADSL variables **TR01PG1/N** to pool treatment

1=MONOTHERAPY

2=COMBINATION THERAPY TYPE A

3=COMBINATION THERAPY TYPE B

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Examples / Templates

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**Table 4a. Cumulative Subject Exposure to IMP from Ongoing and Completed Trials by Age and Gender**

| Age group (Years) | Study Identifier | Male N (%) | Female N (%) | Total N (%) |
|---|---|---|---|---|
| >= 18 - < 45 | [illegible] 2-002 | 1 (100.0) | | 1 |
| | [illegible] 003 | | 2 (100.0) | 2 |
| | [illegible] -004 (Phase I) | 11 ( 57.9) | 8 ( 42.1) | 19 |
| | [illegible] -004 (Phase II) - estimated | | | |
| | [illegible] 006 - estimated | | | |
| | [illegible] -007 | 4 ( 80.0) | 1 ( 20.0) | 5 |
| | Total | 16 (59.3) | 11 (40.7) | 27 |
| >= 45 - < 65 | [illegible] 2-002 | 9 (100.0) | | 9 |
| | [illegible] 003 | 7 ( 50.0) | 7 (50.0) | 14 |
| | [illegible] -004 (Phase I) | 5 ( 45.5) | 6 (54.5) | 11 |
| | [illegible] -004 (Phase II) - estimated | [illegible] ( 51.9) | 37 (48.1) | 77 |
| | [illegible] 006 - estimated | 30 (100.0) | | 30 |
| | [illegible] -007 | 8 ( 47.1) | 9 (52.9) | 17 |
| | Total | 99 (62.7) | 59 (37.3) | 158 |
| >= 65 | [illegible] 2-002 | 16 (100.0) | | 16 |
| | [illegible] 003 | 10 ( 66.7) | 5 (33.3) | 15 |
| | [illegible] -004 (Phase I) | 2 ( 40.0) | 3 (60.0) | 5 |
| | [illegible] -004 (Phase II) - estimated | [illegible] | [illegible] | [illegible] |
| | [illegible] 006 - estimated | 93 (100.0) | | 93 |
| | [illegible] -007 | 3 ( 60.0) | 2 (40.0) | 5 |
| | Total | [illegible] (85.6) | 27 (14.4) | 87 |

Cut off date is Jan 2013
Path: [illegible]Drug_Tasks\DSUR\Primary\TLF\Pgm\T_TAB3.sas
OutputID: T_4a 01FEB2013 16:12

**Estimated=Blinded** studies were allocated to 'random dummy' arm

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Examples / Templates

Cytel Geneva Branch

**Table 4b. Cumulative Subject Exposure to IMP from Ongoing and Completed Trials by Racial Group**

| Race | Study ID | Number of Subjects |
|---|---|---|
| White | [illegible] 002 | 26 |
| | [illegible] -003 | 46 |
| | [illegible] 2-004 (Phase I) | 31 |
| | [illegible] -004 (Phase II) - estimated | 16 |
| | [illegible] 2-006 - estimated | 116 |
| | Total | 335 |
| Black or African American | [illegible] -006 - estimated | 5 |
| | Total | 5 |
| Asian | [illegible] -007 | 27 |
| | [illegible] 004 (Phase II) - estimated | 1 |
| | Total | 28 |
| Native Hawaiian or other Pacific Islander | [illegible] -006 - estimated | 1 |
| | Total | 1 |
| Other | [illegible] 04 (Phase II) - estimated | 2 |
| | [illegible] 006 - estimated | 1 |
| | Total | 3 |

Cut off date is Jan 2013
Path: Drug_Tasks\DSUR\Primary\TLF\Pgm\T_TAB4.sas
OutputID: T 4b 01FEB2013 16:14

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Example / Templates

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**Table R2b. List of treatment emergent death during the reporting period**

| Study ID | Subject ID | Treatment Group | Last Dose Date | Date of death | Cause of death/ Adverse event leading to death (MedDRA Preferred Term) |
|---|---|---|---|---|---|
| -003 | 01-3003 | 1000 mg q2w | 09JUL2012 | 26AUG2012 | Disease progression |
| | 01-3006 | 1000 mg q2w | 03SEP2012 | 01OCT2012 | Disease progression |
| -004 (Phase II) | 01-1006 | Blinded* | 19SEP2012 | 29OCT2012 | Disease progression / Asthenia |
| | 02-1013 | Blinded* | 07AUG2012 | 18SEP2012 | Disease progression / Disease progression |

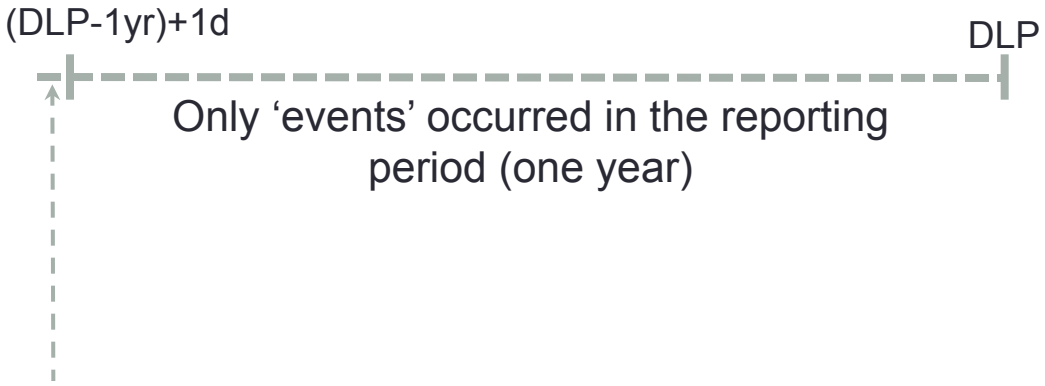
Reporting period: 24 2012 - 23 2013
*Trial team blinded to treatment group to keep the integrity of the study. SoC=Standard of Care
Adverse Events reported using MedDRA Version 15.0
Path: \Drug_Tasks\DSUR\Primary\TLF\Pgm\L_LIST2.sas
OutputID: L_R2b 01FEB2013 16:09

Clear definition / rule to identify death if death form is not available e.g. AE with fatal outcome

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Example / Templates

## By-Period Outputs - Filtering for new «events» or events not yet in db at the time of previous DSUR




- Some «events» (Drop-outs or deaths) may be **not in db at the time of db extract**
- A new «event» is considered new if:
  - Occurred in the **current** DSUR reporting period
  - **Not in db** at the time of previous DSUR

# Implementation in Biostatistics Department

## Type of Outputs to be Provided – Example / Templates

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**Table COMPLIANCE1. Subject compliance to study drug in the reporting period By Study and Treatment**

| Study Identifier | Treatment | Investigational Arm N. of Administration | Investigational Arm % of Compliant Administration | Control Arm N. of Administration | Control Arm % of Compliant Administration |
|---|---|---|---|---|---|
| [illegible]003 | [illegible]10 mg q2w | 12 | 100.0% | | |
| | [illegible]1000 mg q2w | 34 | 100.0% | | |
| [illegible]-004 (Phase II) | SoC ([illegible]) - estimated | | | [illegible]35 | 93.7% |
| | [illegible]500 mg q2w + SoC - estimated | [illegible]53 | 93.3% | | |
| | [illegible]1000 mg q2w + SoC - estimated | 35[illegible] | 88.8% | | |
| [illegible]-006 | Placebo + SoC ([illegible]) - estimated | | | 385 | 95.8% |
| | [illegible]750 mg q3w + SoC - estimated | [illegible]22 | 94.6% | | |
| | [illegible]1500 mg q3w + SoC - estimated | 313 | 94.6% | | |
| | [illegible]1500 mg q3w Open Label* | 82 | 91.5% | | |
| [illegible].7-007 | [illegible]1000 mg q2w | 27 | 96.3% | | |
| | [illegible]1500 mg q2w | 22 | 100.0% | | |

Reporting period: [illegible] Jan 2012 - [illegible] Jan 2013
* Subjects crossing over to experimental treatment after experiencing disease progression.
Path: [illegible]\Drug_Tasks\DSUR\Primary\TLF\Pgm\T_TAB7.sas
OutputID: T_COMPLIANCE1 01FEB2013 16:16

- Additional outputs for compliance
- The way compliance is described depends on the indication and type of therapy
- **Estimated=Blinded** studies were allocated to 'random dummy' arm

# Implementation in Biostatistics Department

## Case 1 – Late Stage Development Project

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- An oncology IMP with active ph 2/3 Trials
  - 18 ongoing/closed trials
  - SDTM available for all trials
  - Because of several SDTM studies managed by the same CRO, cut-off and therefore reporting period was cut by one week
- Reports provided by
  - Indications: NSCLC, Breast, Pancreatic Cancer
  - Type of Combination: Monotherapy, Combination Therapy 1, Combination Therapy 2
- Identification of Adverse Events of Special Interest

Data mapping approach option 1 was used

# Implementation in Biostatistics Department

## Case 2 – Early Stage Development Project

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- Only ph 1/2 Trials
  - 6 ongoing/closed trials
  - SDTM not available for all trials
  - Data Harmonisation entirely performed in ADaM
  - Healthy volunteers ph 1 not included but reported separately
- Reports provided by
  - Dose level of the sponsor IMP
- Blinded studies
  - A dummy randomisatiom arm was used

<u>Data mapping approach option 3 was used</u>

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- **Conclusions**

# Conclusions

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- The new DSUR ICH guidance requires more information / effort than its predecessors
- The new process can be challenging as it requires involvement of several functions and definition of a clear centrally coordinated process
- Use of CDISC principles facilitate harmonisation / data-integration. The DSUR can be seen as a 'pilot' for data integration of a medical product
- SDTM delivery may delay / change internal timeline
- Once implemented it is «easy» to repeat (subsequent DSURs)

# References & Acknowledgments

Development Safety Update Report E2F, Step 4 Version 17 August 2010 (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html)

Adapt and Survive: Implementing the new ICH Development Safety Update Report (DSUR) - P.Gerend R.Sharma – PharmaSUG 2012

# Questions

Cytel

**Angelo Tinazzi**
*Principal Statistical Programmer*

**Cytel Inc.**
Route de Pré-Bois 20
C.P. 1839
1215 Geneva 15, Switzerland
www.cytel.com

T +41 79 535 99 49
angelo.tinazzi@cytel.com

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# Backup Slides

# Background and Overview of the new ICH Guidance

## Background – US IND vs EU Annual Safety Report

| US-IND<br>Based on the IND anniversary date (DIBD) of the IMP | EU-ASR<br>Based on the first authorization of a clinical trial of an IMP by authority in any EU member state |
|---|---|
| Benefit-risk assessment<br>(Cumulative data from DIBD)<br>Indication | Progress Report<br>(Period under review)<br>Molecule |
| Annual | Annual or on request |
| FDA | EU member state authorities<br>Independent Ethics Committees |
| All SAEs | All Serious ARs |
| Narrative or Tabular summary of most frequent AEs<br>List of deaths and drop-outs<br>List completed/Non-Completed studies | Coincise global analysis<br>All new and relevant findings in the period |

# Implications for data management / biometrics departments

## Use of CDISC Principles – Standard Corporate ADaM requirements for DSUR - ADSL

| Derived Dataset Name | Variable Name | Variable Label |
|---|---|---|
| ADSL | STUDYID | Study Identifier |
| ADSL | USUBJID | Unique Subject Identifier |
| ADSL | ARM(N) | Description of Planned Arm |
| ADSL | AARM(N) | Description of Analysis Arm |
| ADSL | TRT01P(N) | Planned Treatment |
| ADSL | TRT01A(N) | Actual Treatment |
| ADSL | TRTSDT | First dose date |
| ADSL | TRTEDT | Last dose date |
| ADSL | SAFFL | Safety Population Flag |
| ADSL | SEX(N) | Sex |
| ADSL | BRTHDT | Birth Date |
| ADSL | AGE | Age |
| ADSL | AGEU | Age Units |
| ADSL | AGEGR1(N) | Pooled Age Group 1 |
| ADSL | RACE(N) | Race |
| ADSL | _INDICATION | Study Indication |
| ADSL | _STDYSTFL | Study Status Flag |
| ADSL | RANDDT | Date of randomization |
| ADSL | COUNTRY | Country |
| ADSL | DTHDT | Date of Death* |
| ADSL | DTHREAS | Cause of Death/Adverse event leading to death (MedDRA Preferred Term) ** |
| ADSL | ESSTAT(N) | End of Study Status |
| ADSL | ESDREAS | Reason for Study Discontinuation |
| ADSL | ESDDT | Study Discontinuation Date |
| ADSL | EXDOSE | Cumulative Actual Dose of Study Drug |
| ADSL | EXPLDOSE | Cumulative Planned Dose of Study Drug |
| ADSL | EXCOMPL | Compliance of Study Drug |
| ADSL | EXYRS | Exposure in Years |

**Notes to programmer:**

•If no Death page is available, but AE/SAE with outcome "fatal" are present in the data base, the DTHDT should be derived based on AE start/end dates

•** If no Death page is available, but AE/SAE with outcome "fatal" are present in the data base, the DTHREAS should be derived as AE MedDRA Preffered Term

•Variables STUDYIDN: "Study Identifier (N)", STRFR1 "Stratification Factor 1", STRFR1N "Stratification Factor 1 (N)" could be added into data set ADSL if required for programming of outputs

# Implications for data management / biometrics departments

## Use of CDISC Principles – Standard Corporate ADaM requirements for DSUR - ADAE

| Derived Dataset Name | Variable Name | Variable Label |
|---|---|---|
| ADSL | STUDYID | Study Identifier |
| ADSL | USUBJID | Unique Subject Identifier |
| ADSL | ARM(N) | Description of Planned Arm |
| ADSL | TRT01P(N) | Planned Treatment |
| ADSL | TRT01A(N) | Actual Treatment |
| ADSL | TRTSDT | First dose date |
| ADSL | TRTEDT | Last dose date |
| ADAE | AESTDT | Adverse Event Start Date |
| ADAE | AESTDTC | Adverse Event Start Date |
| ADAE | AEENDT | Adverse Event End Date |
| ADAE | AEENDTC | Adverse Event End Date |
| ADAE | AEDECOD | Preferred Term |
| ADAE | AEBODSYS | Body System or Organ Class |
| ADAE | AETERM | Reported Term |
| ADAE | AEACT | Action Taken |
| ADAE | AEOUT | Outcome |
| ADAE | TRTEMFL | Treatment Emergent Flag |
| ADAE | AESER | Serious Adverse Event |
| ADAE | AESEV | Severity of AE |
| ADAE | _MEDDRAN | MedDRA Version |