

Standardization in clinical development

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ABSTRACT

This paper discusses a method to maximize the benefits from the various large clinical IT projects many pharmaceutical companies are involved in during these years.

Included is an outline of the clinical standardization organization with its 3 standardization working groups.

It details the standardization work of the Report standardization group:

- Targets defined
- Approach chosen
- Challenges met

INTRODUCTION

The following describes the vision and success factors in Global Development at Novo Nordisk.

The background for the standardization organization and the work of the standardization working groups is described and the targets and approach of one of the working groups is detailed.

BACKGROUND

The main vision for the Global Development organization at Novo Nordisk is to triple the pipeline value.

Critical success factors to reach this target are:

- Support larger increase in patient volumes
- Utilize resources more efficiently
- Leverage data better

To reach this vision several large clinical IT projects have been initiated: development of a clinical data warehouse, electronic data capture, resource portfolio management and clinical supplies IVRS/IWRS management (CSIM).

But implementation of new IT systems and development of new processes are not sufficient.

Standardization is absolutely essential to realize the expected benefits:

- Consistency in the structure and quality of data
- Reductions in time and costs needed for set-up, processing and reporting of data
- Streamlined cross trial reporting and summary reporting
- Improved consistent quality and/or improved compliance
- Improved productivity, reduced cost and/or cycle time
- More effective management of shared and scarce resources



Figure 1: The Data Chain

The Development data chain follows the flow of clinical data points and their attributes

- from their definition in a protocol,
- to their use in CRFs, databases and analyses,
- and through their inclusion in reports and submissions.

By standardization, reusability of data chain components is enabled.

STANDARDIZATION ORGANIZATION

A standardization organization was defined:

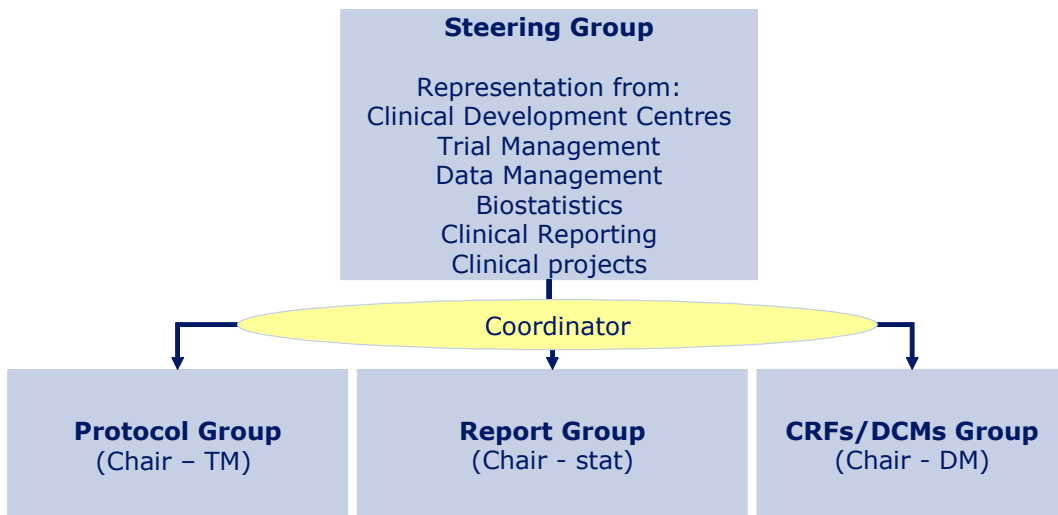


Figure 2: Standardization Organization

Targets for 2005 were set for the 3 working groups:

Working Group	Tasks
Protocol Group	Specification of meta data for protocol, treatment and visit schedule
Report Group	Specifications for 15 standard reports and corresponding derived variables
CRFs/DCMs Group	Specification of standards for case record forms and data collecting modules

Figure 3: Targets for 2005

THE REPORT STANDARDISATION GROUP

In the following section, the work and approach of one of the working groups is detailed.

APPROACH

Selection of generic data areas:

- Categorical findings
- Numerical findings

A finding is a measurement conducted at one or more visits

Numeric findings are measurements with a numeric result type – ex. vital signs, some laboratory assessments, pulmonary function tests, etc.

Categorical findings are measurements with a categorical result type – ex. physical examinations with the results normal/abnormal.

Selection of data domains:

- Physical Examination
- Vital Signs
- ECG
- Laboratory Tests
- Subject Disposition
- Baseline Characteristics

Investigation of common types of reports to make for these data domains:

- Summary tables
- Change from baseline tables
- Shift tables
- Listings
- Individual subject plots
- Mean plots
- Scatter plots
- Box and Whiskers plots
- Histograms

REPORT TEMPLATES

Report templates are high level layout decisions documents which are used as basis for the design of the single reports such as Summary of Physical Examination at Baseline, Shift Table of Hematology, etc.

A report template was made for each of these report types – for some of them both a template for numeric and categorical findings were made.

Report templates were prepared for table, listing and figure templates with layout decisions.

General layout definitions:

- Page orientation (portrait or landscape)
- Font(s) to use
- Page size (number of lines per page, number of characters per line)
- Title (number of lines, alignment, space before/after title, standard titles)
- Footnotes (number of lines, alignment, automatic definition of abbreviations, user defined footnotes)
- Footer (alignment, components: trial, instance, program name, output name, execution date and time, executed by)
- For figures (symbols, line types, colors, labels, axes)
- For tables/listings (mandatory/optional columns, lines before/after column headings, column headings, alignment of columns, labels, mandatory/optional statistical variables, optional blocks)

Report templates were defined for the generic data types and data domains:

Tables of numeric findings:

Summary of [parameter] <at [visit description]> by Treatment – [Analysis Set]<, [subpopulation selection criteria]>
Summary of [parameter] ([unit]) by <Visit and> Treatment – [Analysis Set]<, [subpopulation selection criteria]>

Tables of categorical findings:

Summary of [parameter] <at [visit description]> by Treatment – [Analysis Set]<, [subpopulation selection criteria]>
Summary of [parameter] by <Visit and> Treatment – [Analysis Set]<, [subpopulation selection criteria]>
Change <(absolute)><(relative)> from [visit description for baseline visit] of [parameter] ([unit]) by Treatment – [Analysis Set]<, [subpopulation selection criteria]>
Shift Table for [parameter] – [Analysis Set]<, [subpopulation selection criteria]>

Plots of numeric findings:

[parameter] ([unit]) by Time, Mean – [Analysis Set]<, [subpopulation selection criteria]>
<Individual><Multiple> Subject Line Plot of [parameter] ([unit]) by Time – [Analysis Set]<, [subpopulation selection criteria]>
Scatter Plot of [parameter1] ([unit1]) vs. [parameter2] ([unit2]) at [visit description] – Analysis Set<, [subpopulation selection criteria]>
Box and Whiskers Plot of [parameter] ([unit]) by <Visit and> Treatment – [Analysis Set]<, [subpopulation selection criteria]>

criteria]>

Frequency of [parameter] <at [visit description]> – Analysis Set<, [subpopulation selection criteria]>

Listings of numeric and/or categorical findings:

[Parameter] – [Analysis Set]<, [subpopulation selection criteria]>

REPORTS

Based on the report templates the following reports were made:

Summary of Baseline Characteristics by Treatment – ITT Analysis Set
 Summary of Physical Examination at Baseline by Treatment – Safety Analysis Set
 Summary of Haematology at Baseline by Treatment – ITT Analysis Set
 Summary of Haemoglobin (mmol/L) by Visit and Treatment – ITT Analysis Set
 Change (absolute) from Baseline of Haemoglobin (mmol/L) by Treatment – ITT Analysis Set
 Summary of Vital Signs at Baseline by Treatment – Safety Analysis Set
 Summary of Pulse, Sitting (beats/min) by Visit and Treatment – Safety Analysis Set
 Summary of ECG at Baseline by Treatment – ITT Analysis Set
 Summary of ECG by Visit and Treatment – ITT Analysis Set
 Shift Table for ECG – ITT Analysis Set
 Weight (kg) by Time, Mean - ITT Analysis Set
 Box and Whiskers Plot of Albumin (g/L) by Visit and Treatment – ITT Analysis Set
 HbA1c (%) by Time, Mean - ITT Analysis Set
 Scatter Plot of Insulin Detemir Specific Antibodies (%B/T) at Baseline vs. End of Trial (24 weeks) – ITT Analysis Set
 ECG Findings – ITT Analysis Set
 Haematology Laboratory Test Results Outside Reference Range – ITT Analysis Set
 Physical Examination Findings – Safety Analysis Set
 Abnormal Vital Signs – Safety Analysis Set

An example of a report:

VS_T002: Summary of Pulse, Sitting (beats/min) by Visit and Treatment – Safety Analysis Set

	Treatment1	Treatment2	Comparator	Total
Number of Subjects	xxxx	xxxx	xxxx	xxxxx
Visit 2 Baseline				
N	xxxx	xxxx	xxxx	xxxxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
Visit 5 End of Treatment (6 weeks)				
N	xxxx	xxxx	xxxx	xxxxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x
Change (absolute) from Baseline to End of Treatment (6 weeks)				
N	xxxx	xxxx	xxxx	xxxxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x	xx.x	xx.x
Min ; Max	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x	xx.x ; xxx.x

SD: standard deviation

<Therapeutic Area>/<Clinical Programme>/<project>/<trial>/<instance>
 <date> – <programme name>/<output name>

BUSINESS RULES

Business rules for creating the variables used in the reports or for manipulation of the data points were defined. To cover the needs for the reports created 67 business rules were defined. Examples of some of these are:

Age at Baseline**Description:**

Age calculated at the baseline visit using the date of birth and baseline visit date. Measured in years.

Use:

Will be used for the demography dataset.

Data type:

Float

Algorithm:

age = yrdif(birth date,baseline visit date,'ACT/ACT')

'ACT/ACT': uses the actual number of days between dates in calculating the number of years. SAS calculates this value as the number of days that fall in 365-day years divided by 365 plus the number of days that fall in 366-day years divided by 366.

Visit Reallocation**Description:**

Use of unscheduled and planned visits. Check of whether visits are within time windows are used to find the best measurement to use.

Use:

Can be used in all dataset.

Data type:

NA

Algorithm:

For every measurement date with a valid result check against time windows from flow chart.

If measurement date is within time window then assign measurement to the visit.

Flow chart

Visit	1 - Screening	2 - Baseline	3 – 3 months	4 – 6 months
Time	- 2 weeks $\pm$ 3 days	0 weeks	12 weeks $\pm$ 7 days	24 weeks $\pm$ 7 days

Measurement data

Subject ID	Visit ID	Measurement date	Measurement result
1001	1	01MAR2005	<valid>
1001	2	14MAR2005	<valid>
1001	3	14JUN2005	<not valid>
1001	Unscheduled	20JUN2005	<valid>
1001	Unscheduled	10SEP2005	<valid>
1001	4	16SEP2005	<valid>

After applying visit reallocation 2 rule

Subject ID	Visit ID	Measurement date	Measurement result
1001	1	01MAR2005	<valid>
1001	2	14MAR2005	<valid>
1001	3	20JUN2005	<valid>
1001	4	10SEP2005	<valid>
1001	4	16SEP2005	<valid>

Partial Date**Description:**

Can be used to impute the full date from a partial date. Rules will be defined per parameter. This can as an example be used for birth date.

Use:

Can be used for all datasets.

Data type:

Integer (SAS date)

Algorithm:

dd missing: day part set to: 01

ddmmm missing: day and month part set to: 01JUL

Full Analysis Set (FAS)

Description:

The full analysis set is defined according to the ICH Guideline E9.

Full analysis set including all randomised subjects who fulfil the criteria:

have taken at least one dose of trial medication (that is, exposed subjects)

have data post randomisation

The analysis set build on the ITT principle and the subjects will be analysed as randomised.

Variable should be a flag variable with the values 'Y' or 'N'. In the definition in E9 it is also possible to exclude subjects from the population due to major eligibility violations, but these must be made on a trial by trial basis and specified in the SAP.

Use:

Flag variable to merge on all datasets.

Data type:

Char1.

Algorithm:

```
if randomised='Y' and exposed='Y'  
    and max_visit > visit(randomisation) then fas='Y';  
else fas='N';
```

IMPLEMENTATION

The defined report templates, reports and business rules are fed into the clinical data warehouse project to be implemented there. The report templates and reports are implemented as standard programs to be used by the clinical projects to report their data, while the business rules are implemented as a library of standard programs to apply to the data in the data warehouse in order to define extra variables or manipulate the data. In the set-up of the single trial in the data warehouse decisions will be made on which business rules to apply depending on the type of trial and the data.

TARGETS FOR THIS YEAR

Targets for 2006:

- Reports for all standard CRFs (report templates, reports, business rules)
- Reports for events (report templates, reports, business rules for AEs, Hypos, Time to final height, etc)
- Analysis tables (types of analyses, models, assumptions, report templates, reports, business rules)

CHALLENGES MET

Implementing standards in a global organization can be a difficult task. The opinions are many and the requirements from the health authorities can differ. So a certain amount of flexibility will be required, to ensure that the standards are actually used in the daily work.

An organization taking care of the development and maintenance of the standards is needed – with procedures for decision taking, documentation, change management and communication.

Another recurrent challenge is the project set-up of the standardization work groups. All work group members are allocated part time (10 – 40 %) to the standardization work and the rest of the time to clinical projects. This set-up has been established to ensure the relevance of the output to the different clinical projects and to facilitate the buy-in from the different clinical project groups. A negative effect of such an arrangement is that it can be very difficult for group members working on busy clinical projects with tough deadlines to free time to do the standardization work. So even though the project allocations look fine on paper, the reality shows a different picture.

CONCLUSION

To start implementing global standards at Novo Nordisk Global Development has been a major challenge, but it has also been fun. The success of such a project depends both on the support in the organisation and the timing. At Novo Nordisk Global Development the management has supported the standardization work, but the acceptance and support from the people, who will use the standards, is even more important. Caused by the growth in our business, the many new projects both within the clinical and IT area, the increased amount of trial data to manage, the increased amount of statistical analyses

to conduct and reports to generate, the need of changes and standardization has been recognised by my colleges in the organization.

An important point to realise is that even though we finalise the projected standardisation work for this year the standardisation work will never be final. It will be an ongoing task.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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