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From Local Laboratory to Standardisation and beyond
Applying a common grading system

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ABSTRACT

Data Management of Laboratory Data, such as haematology and biochemistry, can be very time consuming, especially when data are collected in different local laboratories, all of them with different normal ranges and units. This is the standard situation in oncology, where patients usually have their blood samples drawn outside the hospital, after being discharged or when therapy is administered at home.

The present paper will review the full process of dealing with such data, and the application of a common grading system, the CTCAE grading system, will be also described.

INTRODUCTION

Most clinical trials collect laboratory data. The procedures for biological samples processing and the amount of laboratory data collected can be very different depending on the type of trial[1].

Laboratory tests performed within clinical trials in oncology are used both to make immediate clinical decisions for patient's care and to define the drug profile according to the trial objectives.

Early oncology clinical trials, which are often performed in a population with advanced disease in centres of excellence serving a broad geographical area and testing toxic compounds, require frequent samplings, and laboratory results must be available to the treating physician in a very short time for quick decision making; as a consequence, the use of multiple local laboratories cannot be avoided mainly for patients convenience. The results are thus obtained using different equipments and assays which make reference to different ranges of normality and are expressed in different units. This heterogeneity implies great efforts to collect a series of different normal ranges and the need for some methods of conversion to ensure comparability of results.

The aim of this paper is to discuss different methods of data homogenization, trying to identify the most efficient ones in the context of early oncology studies.

LABORATORY TESTS FOR DRUG SAFETY MONITORING

Laboratory tests in clinical trials can be used for safety, activity, pharmacodynamic, pharmacokinetic, pharmacogenomic assessments but for the purpose of this paper we will focus on hematology and blood biochemistry parameters for which the use of central laboratories is usually not feasible.

PARAMETERS COMMONLY USED IN CLINICAL TRIALS

Laboratory results can be expressed with a quantitative numeric or semi-quantitative value (i.e. trace) or qualitative value (i.e. +/-). For most hematology and biochemistry tests, the results are expressed with quantitative numeric values.

Common parameters measured for hematology are:

- Hematocrit;
- Hemoglobin;
- Platelets;
- Red Blood Cells (RBC);
- White Blood Cells (WBC) with differential count for Neutrophils, Lymphocytes, Monocytes, Basophils and Eosinophils

For the chemistry, the most common collected parameters are the following:

- Electrolytes
  - Sodium;
  - Potassium;
  - Magnesium;

- Calcium;
- Chloride;
- Bicarbonate.

- Enzymes
  - Aspartate Aminotransferase (AST/SGOT);
  - Alanine Aminotransferase (ALT/SGPT);
  - Gamma Glutamyl Transferase (γGT);
  - Alkaline Phosphatase;
  - Troponin I;
  - Creatine Phosphokinase (CPK);
  - Lactate Dehydrogenase (LDH).
- Biological Byproduct Test
  - Glucose;
  - Blood Urea Nitrogen (BUN);
  - Creatinine;
  - Total Bilirubin.

CLINICAL INTERPRETATION

Together with the numerical outcome of sample analysis, the investigator can provide some clinical interpretation of any abnormal values (usually defined as value not within normal range). The judgment can be categorized, for example as "Not Clinically Significant", "Clinically Significant (Adverse Event)".

CENTRAL VS LOCAL LABORATORIES

The advantage of using central laboratories is clear, and in particular:

- standardisation of methodology and calibration;
- a unique normal range for all samples;
- electronic transfer of lab data;
- no transcription errors.

while for local laboratories the advantages can be:

- samples can be taken anytime/anywhere (i.e., more convenience for ambulatory patients);
- no transport issue;
- low costs.

Although the advantages of using central labs are pretty clear, in trials like the ones we are considering in this paper, they might not represent a viable solution.

COMMON ISSUES IN MANAGING LABORATORY DATA WITH LOCAL LABORATORIES

Figure 1 describes the main steps in managing clinical trial data when local laboratories are used.

Laboratory results and relevant normal ranges from local Laboratories are collected and stored in the hospital file. Laboratory data are then transcribed onto the CRFs that are sent to the data manager for data processing (the process can be slightly different if a remote data-entry system is used).

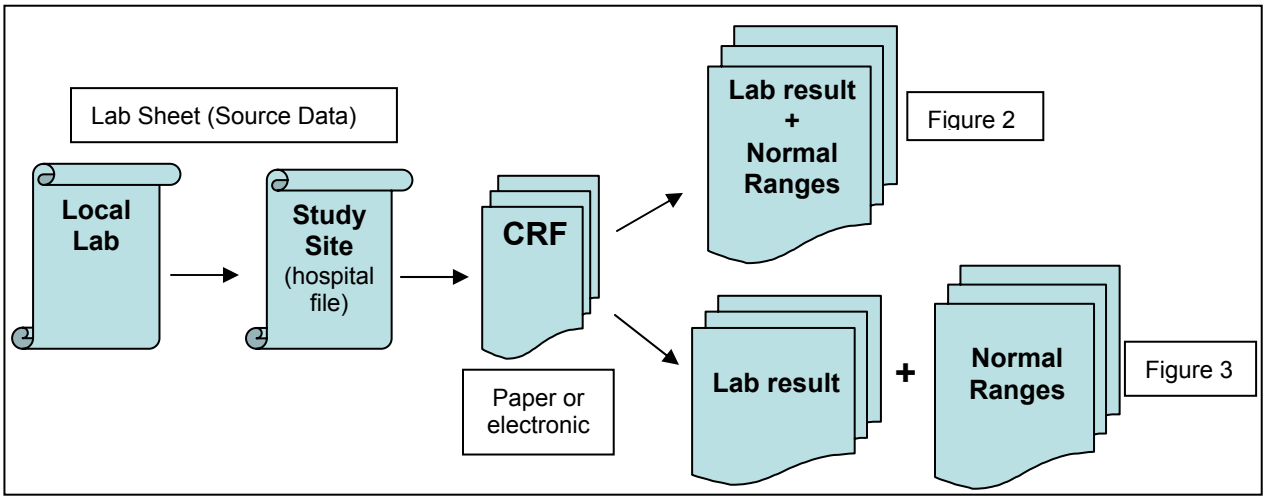
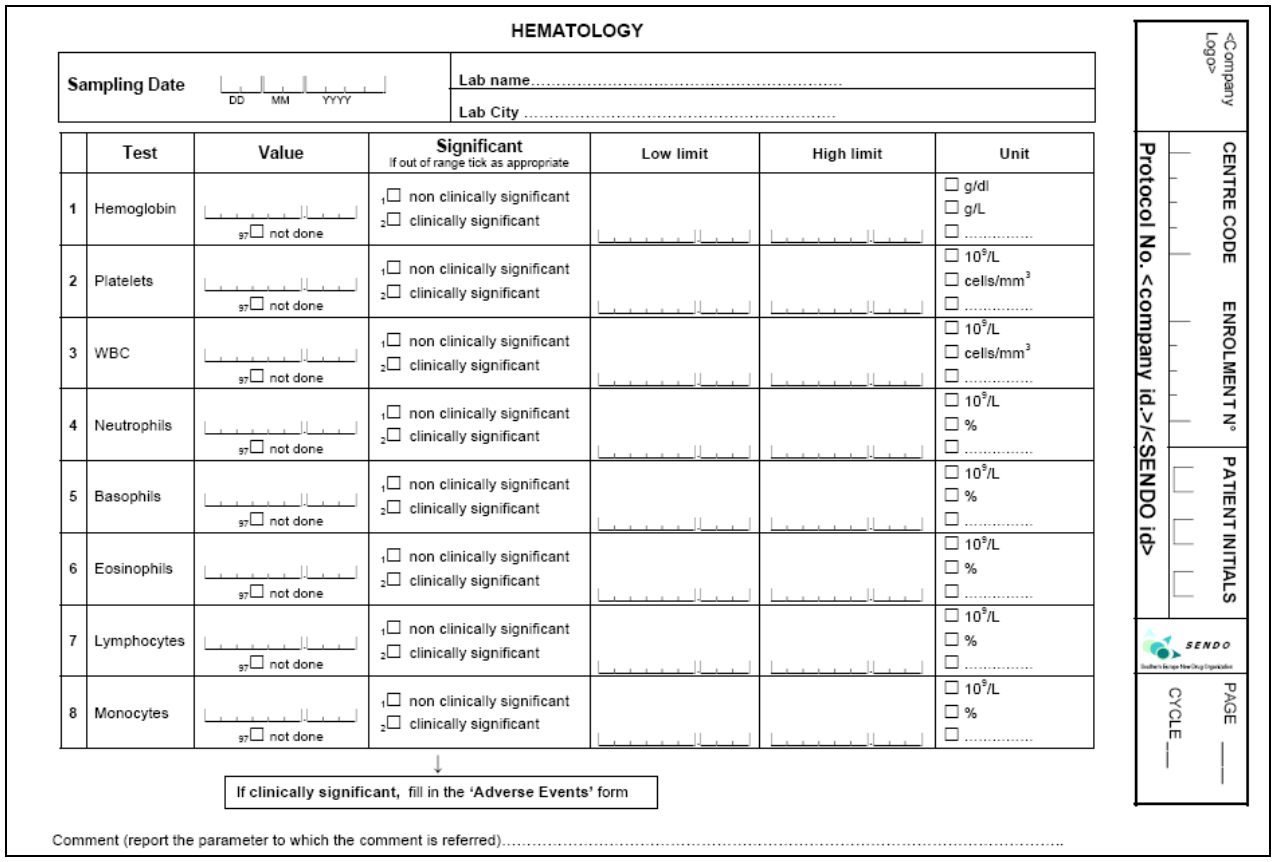


Figure 1: Local Labs Data-Management Process



HEMATOLOGY

Sampling Date DD MM YYYY | Lab name..... | Lab City .....

	Test	Value	Significant (If out of range tick as appropriate)	Low limit	High limit	Unit
1	Hemoglobin	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ g/dl ☐ g/L ☐ .....
2	Platelets	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ cells/mm^3 ☐ .....
3	WBC	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ cells/mm^3 ☐ .....
4	Neutrophils	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ % ☐ .....
5	Basophils	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ % ☐ .....
6	Eosinophils	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ % ☐ .....
7	Lymphocytes	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ % ☐ .....
8	Monocytes	97☐ not done	1☐ non clinically significant 2☐ clinically significant			☐ 10^9/L ☐ % ☐ .....

If clinically significant, fill in the 'Adverse Events' form

Comment (report the parameter to which the comment is referred).....

<Company Logo>

CENTRE CODE ENROLMENT N° PATIENT INITIALS

Protocol No. <company id.>/<SENDO id>

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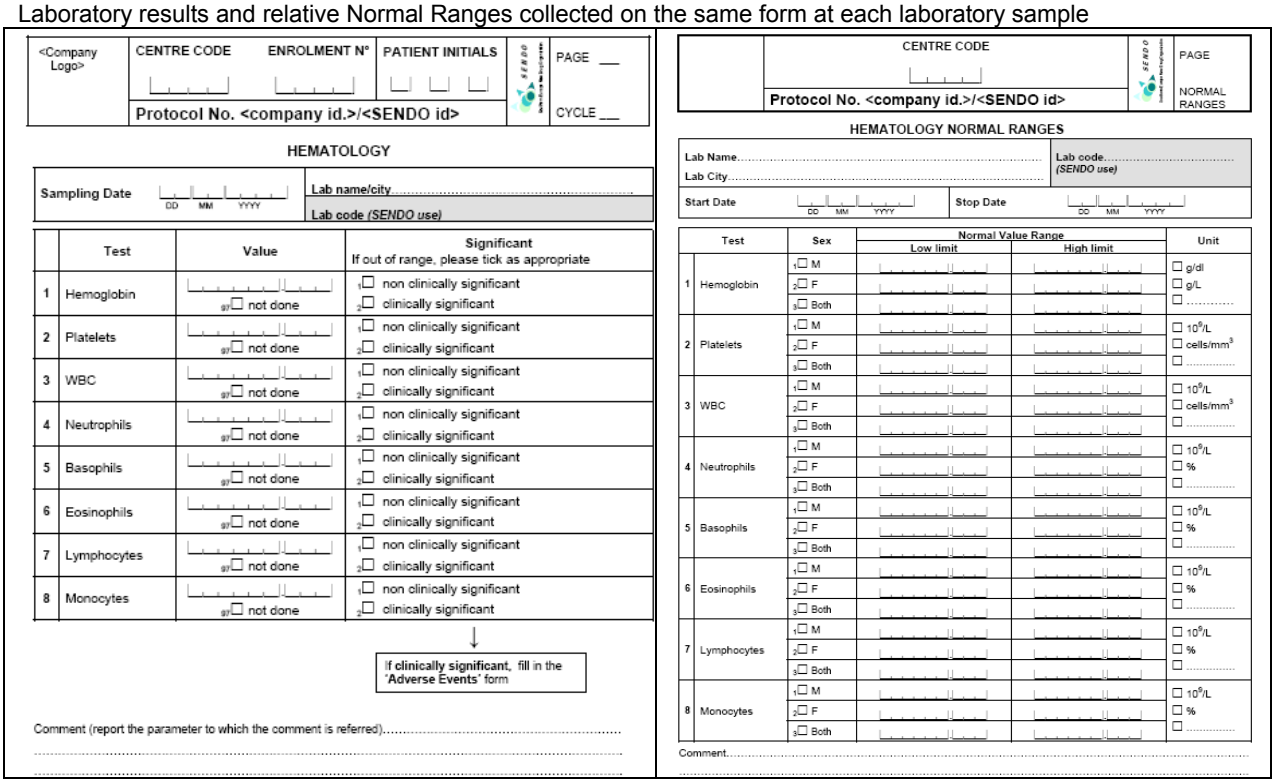
Figure 2: SENDO Standard CRF Version 1

Laboratory results and relative Normal Ranges collected on the same form at each laboratory sample



<Company Logo> | CENTRE CODE | ENROLMENT N° | PATIENT INITIALS | PAGE ___ | CYCLE ___

Protocol No. <company id.>/<SENDO id>

HEMATOLOGY

Sampling Date DD MM YYYY | Lab name/city..... | Lab code (SENDO use)

	Test	Value	Significant (If out of range, please tick as appropriate)
1	Hemoglobin	97☐ not done	1☐ non clinically significant 2☐ clinically significant
2	Platelets	97☐ not done	1☐ non clinically significant 2☐ clinically significant
3	WBC	97☐ not done	1☐ non clinically significant 2☐ clinically significant
4	Neutrophils	97☐ not done	1☐ non clinically significant 2☐ clinically significant
5	Basophils	97☐ not done	1☐ non clinically significant 2☐ clinically significant
6	Eosinophils	97☐ not done	1☐ non clinically significant 2☐ clinically significant
7	Lymphocytes	97☐ not done	1☐ non clinically significant 2☐ clinically significant
8	Monocytes	97☐ not done	1☐ non clinically significant 2☐ clinically significant

If clinically significant, fill in the 'Adverse Events' form

Comment (report the parameter to which the comment is referred).....

CENTRE CODE | PAGE

Protocol No. <company id.>/<SENDO id> | NORMAL RANGES

HEMATOLOGY NORMAL RANGES

Lab Name..... | Lab code..... (SENDO use)

Lab City.....

Start Date DD MM YYYY | Stop Date DD MM YYYY

	Test	Sex	Normal Value Range Low limit	Normal Value Range High limit	Unit
1	Hemoglobin	1☐ M 2☐ F 3☐ Both			☐ g/dl ☐ g/L ☐ .....
2	Platelets	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ cells/mm^3 ☐ .....
3	WBC	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ cells/mm^3 ☐ .....
4	Neutrophils	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ % ☐ .....
5	Basophils	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ % ☐ .....
6	Eosinophils	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ % ☐ .....
7	Lymphocytes	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ % ☐ .....
8	Monocytes	1☐ M 2☐ F 3☐ Both			☐ 10^9/L ☐ % ☐ .....

Comment.....

Figure 3: SENDO Standard CRF Version 2

Laboratory results and Normal ranges collected on separate forms

NORMAL RANGES

Normal ranges, or reference ranges, are used to determine if a person's value is "normal". The 'normal range' for a given constituent of clinical interest is considered to be the concentrations of the constituent which are found in the body fluid or excretions of a group of clinically normal persons.

For the same parameter different normal ranges can be applicable to different populations, defined by demographic characteristics or other conditions, such as:

- gender (males/females);
- age (children/adults, 30-50 years, etc.);
- fasting/non fasting.

In addition, when analyzing normal ranges variability, also the following issues have to be considered:

- the kit used for the lab analysis, which also provide the relevant normal range, have an expiry date after which a re-calibration procedure has to be performed, which results in the definition of a new normal range (intra-laboratory variability);
- analysis methods can change within a laboratory (intra-laboratory variability).

COLLECTING THE DATA

When planning the data collection tool for a clinical trial, either paper based (CRF) or electronic (eCRF), the way the normal ranges will be collected should be defined. Two main options are available if data cannot be obtained in electronic format from the lab:

- collected with each laboratory value on CRF (Figure 2);
- collected in a separate form linked to all results obtained in the same laboratory during the validity period of the range through an identification code (Figure 3).

If laboratory data are collected using the model shown in Figure 3 a unique lab identification code is assigned to each set of normal ranges. The code is usually assigned by the data manager and it has to be reported both on the 'Lab findings' form and on the Normal Ranges form. The results are then matched with their relative ranges by the laboratory code and possibly other characteristics such as sex and age (usually by the automatic script in the system used for colleting the study data). A 'Start date' is also collected that is the validity start date for those ranges when for any reason one of the parameters changes (e.g. different methods, calibration of the instrument), the current ranges are no longer valid and they are replaced with the new ranges that will have a different lab code and of course a new start date (validity date).

At SENDO, the Normal Ranges and the laboratory codes are managed across studies and projects: in case the same laboratory is in use in different studies, the same code is maintained for the laboratory, regardless of the study in which it is applied. With this approach, issues that arise are tracked centrally and managed consistently across the studies.

In the situation of local laboratories providing data by means of electronic files, additional problems should be taken into consideration; Szilagyi and Binder[2] have discussed some of the issues inherent the electronic data transfer from the central/local laboratories, describing the type of interventions required with particular attention to SAS® techniques.

To give you an idea of the implication on data-management with such a variety of variables, we have analysed normal ranges applied to four recent clinical trials conducted at SENDO, three phase I and one phase II (table 1). On average every patient has used two different local laboratories (the average was greater in phase I studies), with a maximum of seven local laboratories used by the same patient.

Another important data emerging from table 1 is the number of different local laboratories used for each trial. Apart from the phase II study, the nr. of local laboratories was greater than the number of patients enrolled, which highlights the heterogeneity of laboratories used, considering also the fact that the three phase I trials were conducted in four investigational sites in total. However, the impact of this statistics diminishes with the adoption in SENDO of a central repository of local laboratory dictionary, where each local laboratory is identified only once across all the studies, and we expect this impact will be even lower with the dictionary size increase; in fact about 20% of local laboratories identified in the SENDO dictionary was used in more than one clinical trial (97 local laboratories identified in the central repository vs 119 local laboratories used in the four different clinical trials).

Study Nr	Nr. of Patients	Nr. of samples collected (average nr by Patient, min-max)	Nr. of Different Local Labs Used	Average Nr. of Local Labs Used by each patient (min-max)
1 (ph I)	34	37 (2-90)	44	3.0 (1-7)
2 (ph I)	32	27 (2-79)	33	2.7 (1-6)
3 (ph I)	20	24 (2-61)	31	2.8 (1-5)
4 (ph II)	38	14 (2-33)	11	1.4 (1-3)
Overall in SENDO Repository			97	

Table 1: Local Lab used statistics from four clinical trials conducted at SENDO

One additional statistics emerging from our analysis, is the number of different units applied. Overall 34 different units were identified across all parameters, with higher variability in haematological parameters (15 for WBC, 14 for platelets, 12 for neutrophils), whereas for chemistry only Albumin used more than three units (4). Table 2 shows the list of units used to report Platelets Count.

/MM3	10E6/ML
/UL	10E9/L
10E3/CL	CELLS/MM3
10E3/MCL	G/L
10E3/MM3	GIGA/L
10E3/MMC	MM3/10E3
10E3/UL	XMMC

Table 2: Units used for reporting Platelets count in 97 different local laboratories

QUALITY CONTROL

Managing clinical laboratory data can pose specific challenges for clinical data managers, especially because most of the parameters collected are represented by a continuous scale determining an infinite number of possible values. Laboratory data are more difficult to interpret if one does not have specific clinical training, and what is appropriate to query is less clear, especially because the potential for error with this model is very high. Several types of errors can be detected:

- missing data: unit, value, clinical interpretation, etc.;
- hand-writing legibility: is it "1.17" or "1.11"?
- inconsistency between value and unit: an abnormal value can be due to a wrong reporting of the relevant unit, for example should gram/L actually be grams/dL? should the neutrophils unit be "%" instead of "10^9/L"? (see example in figure 4).

The logical checks (edit checks in computer language) are used to compare the laboratory values to the normal ranges provided by the site (local laboratory). A particular check is the one to identify errors in White Blood Cells (WBC) differential count: when differential count parameters are reported in %, these should sum up to 100±X%, usually 3% (figure 5); or if reported as absolute count (e.g. 10^9/l), these should sum up to the total WBC±X (figure 6).

18 10^9/L ↑
abnormal high (e.g. patient with an active infection)

18 % with "1" 10^9/L WBC, Neutrophils count is transformed to 0.18 10^9/L ↓
abnormal low (hematological toxicity)

Figure 4: Is it the Neutrophils unit correctly reported?

Neutrophils	2.48	
Basophils	0.01	
Eosinophils	0.06	
Lymphocytes	0.43	
Monocytes	0.10	
TOTAL	*3.08*	*which correspond to X% of WBC reported in the CRF (3.10)*

Figure 5: White Blood Cells Count Example (values reported as 10^9/L)

Neutrophils	80.0	converted to 2.48 10^9/L, that is 80.0% of 3.10
Basophils	0.3	converted to 0.01 10^9/L, that is 0.3% of 3.10
Eosinophils	1.9	converted to 0.06 10^9/L, that is 1.9% of 3.10
Lymphocytes	13.9	converted to 0.43 10^9/L, that is 13.9% of 3.10
Monocytes	3.2	converted to 0.10 10^9/L, that is 3.2% of 3.10
TOTAL	*99.4*	

Figure 6: White Blood Cells Count Example (values reported as %)

Logical checks may be not always appropriate and they may not be able to detect particular situation. It is therefore useful to add specific reports for helping the clinical data-manager in the review of the laboratory data, especially at the end of the study when it is important that every single step in the laboratory data management is completed:

- every laboratory value should have its corresponding unit;
- the SI unit derivation (see next section);
- when applicable the CTCAE calculation (see next section).

It can be for example useful to have some graphical display to quickly identify outliers or the same can be done by reporting for each laboratory test, across patients, the first and last values falling in the 10% and 90% percentiles respectively. If this is done using SAS, the method reported in figure 7 can be applied.

proc sort data=lab out=outliers;
  by lbtest lbsval;
run;
data outliers;
  by lbtest lbsval;
  retain nval1 nval2 0 first last .;
  if first.lbtest then do;
  first=.; last=.; nobs=0;
  nval1=max(15,int(nval*(&PCTOUT/100)));
  nval1=min(100,nval1);
  nval2=int(nval*(1-(&PCTOUT/100)));
  nval2=max(nval,nval-100);
  if nval-nval2<15 then nval2=nval-15;
  end;
  if _N_ le nval1 then do;
  if first eq . then do;
  first=1;
  fp=1;
  end;
  output;
  end;
  else if _N_ ge nval2 then do;
  if last eq . then do;
  last=1;
  fp=1;
  end;
  output;
  end;
run;
/**** Proc Report here ****/
	Sort the dataset by test (LBTEST) and SI Lab Value (LBSVAL)
	
	Nval1 / Nval2 are used to count how many 'lower' and 'higher' outliers have been selected
	
	Nval1 / Nval2 are set in order to detect how many records need to be selected (a % of or the first / last '15' if the sample is not big enough)
	
	Observation '_N_' <= nval1 will be kept and reported
	
	Observation '_N_' >= nval2 will be kept and reported

Figure 7: Outliers Detection

STATISTICAL ANALYSIS OF LABORATORY DATA

The Analysis plan should drive analysis programming. Examples of possible analysis of laboratory data include shift tables (e.g. changes over baseline, either as absolute value or as percentage), correlations and time-to-event definition.

In order to perform such analysis, additional steps involving data-manipulation by means of derived variables creation should be planned, so that the results obtained from different local laboratories, can be weighted, summed and more in general compared, as appropriate. Various approaches are hereby illustrated.

CONVERSION TO STANDARD INTERNATIONAL UNIT

The main rationale for the conversion to the 'Système International d'Unités' (SI units) is to ensure that laboratory values from all the local laboratories are converted to the same unit, which is the first step towards comparability across laboratories. In addition in some cases the adoption of the SI units will also simplify and uniform the way the data are reported, so that for example quantifying the amount of a substance in moles (SI units) rather than in grams (traditional units) may also confer a scientific advantage, allowing for an easier understating of molecular relationship.

To convert between original and SI units, conversion factors should be applied[3]. For example, if a laboratory analyses potassium using the mg/dL unit, to convert the value in the SI unit, that is mmol/L, the multiplication factor of 0.2558 should be applied, so that a potassium value of 13.7 mg/dL can be transformed in 3.5 mmol/L.

NORMALISATION

The simple conversion to SI unit does actually not represent a true homogenization of results obtained from different local laboratories using different methods. To ensure a full comparability several techniques have been proposed[4,5,6].

One of the solutions proposed suggests the use of a standard laboratory, that can be either a real laboratory or a theoretical convention, to 'normalize' all laboratory values against a standard normal range.

The method requires the application of a normalization formula ('location-scale') as follows:

$$s = L_s + (x - L_x)\frac{U_s - L_s}{U_x - L_x}$$

where s= the transformed individual laboratory value to a common standard laboratory reference range; x=the original value; Lx and Ux=lower and upper limits of normal range for an individual local laboratory parameter test; Ls and Us lower and upper limits for the selected common standard laboratory (or theoretical / phantom laboratory).
For example let's assume a value of 10 was obtained from local laboratory A with a normal range of 5-25, if we want to normalize this value using the standard laboratory range, that was established to be 10-35, by applying the above formula we would obtain a normalized value of 16.25 as detailed here below

$$s = 10 + (10 - 5)\frac{35 - 10}{25 - 5} = 16.25$$

To calculate the standard laboratory, for example Ruvuna et al[4] on his paper proposed to use the 'percentile' method, which uses normal ranges from several local laboratories (around 100) to create a "phantom laboratory of normal reference ranges"; the method consists of taking the single limits (lower and upper) of all selected normal ranges, ranking them, and taking the 10th and the 90th percentiles.

APPLYING A COMMON GRADING SYSTEM: THE CTCAE

An additional option for analysing laboratory data is the use of a system to categorize laboratory data expressed using continuous scales. The NCI Common Terminology Criteria for Adverse Events – CTCAE (v3.0)[7] is a standard language for reporting adverse events (AE) occurring in cancer clinical trials, but it has a broad use also in other medical fields. The system is organized in categories that are a broad classification of AEs based on anatomy and/or pathophysiology (table 3). An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is also mapped to a MedDRA term and code. AEs are listed alphabetically within categories.

Allergy / Immunology	Gastrointestinal	Ocular / Visual
Auditor / Ear	Growth and Development	Pain
Blood / Bone Marrow	Hemorrhage / Bleeding	Pulmonary / Upper Respiratory
Cardiac Arrhythmia	Hepatobiliary / Pancreas	Renal / Genitourinary
Coagulation	Infection	Secondary Malignancy
Constitutional Symptoms	Lymphatic	Sexual / Reproductive Function
Death	Metabolic / Laboratory	Surgery / Intra-Operative Injury
Dermatology / Skin	Musculoskeletal / Soft Tissue	Syndromes
Endocrine	Neurology	Vascular

Table 3: CTCAE Categories

The CTCAE classify the severity of adverse events by assigning a value ranging from 0 (no toxicity) to 4 (severe toxicity), with the addition of code 5 for severe toxicity causing death. The classification can be based on either qualitative or quantitative evaluation.
For example for Arthritis, where the severity is determined using a qualitative classification, a grade 1 is defined as "Mild pain with inflammation, erythema, or joint swelling, but not interfering with function" and grade 4, the worst severity grade level before the generic 5=death, is defined as "Disabling". Instead Diarrhea, where the severity is determined using a quantitative classification, define the severity grade by quantifying the number of stools per day, that is for example grade 1 defined as "Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline".
Laboratory abnormalities belong to the 'quantitative' adverse events severity classification. For example 'Platelets' adverse event grade 2 is defined as an observed value between 75.000/mm3 (not included) and 50.000/mm3 (see full severity classification in table 4), regardless of the normal range of the specific laboratories.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<LLN – 75,000/mm3 <LLN – 75.0 x 10^9 /L	<75,000 – 50,000/mm3 <75.0 – 50.0 x 10^9 /L	<50,000 – 25,000/mm3 <50.0 – 25.0 x 10^9 /L	<25,000/mm3 <25.0 x 10^9 /L	Death

Table 4: CTCAE Classification for Platelets Count

To make clearer the full process from local laboratories to CTCAE classification through the various required steps, figure 8 describes the 'full story' of a platelets value obtained from a local laboratory.

From the example you can observe the impact of the specific normal ranges is only on definition of grade 0 and 1, while more severe abnormalities (grade>=2) are defined independently from the local laboratories normal ranges.

Observation Nr	1	2	3
Original lab value	120	125.000	15.000
Laboratory Id Nr.	1231	1243	1451
Local Lab Unit	10^9 /L	mm3	mm3
Local Lab Range	110-450	130-470	100-450
SI Standardisation	10^9 /L	10^9 /L	10^9 /L
Conversion factor to be applied	*1	/1000	/1000
Lab value converted to SI unit	120	125	15
CTCAE Grade	0	1	4

The value is above 75x10^9 /L and within normal range, therefore it is classified as 0

The value is above 75x10^9 /L but not within normal range, therefore it is classified as 1

Figure 8: An Application of CTCAE to Platelets Count on three different situations

SPECIAL TOPICS IN THE USE OF LABORATORY DATA IN PHASE I TRIALS IN ONCOLOGY

An additional analysis of laboratory data in oncology, especially for the definition of the toxicity profile (e.g. neutrophils and platelets for hematological toxicity) in the early development of cytotoxic drugs (phase I), is the evaluation of the toxic effects of the drug over time. For example a commonly analyzed parameter is the time to nadir, i.e. the time elapsing from treatment / cycle start to the observation of the lowest value. Similarly also time to recovery to a defined threshold is often determined; for example, if a drug is administered once every 28 days (that is the cycle duration), we may be interested to see when the most severe toxicity is to be expected (time to nadir) and what is the duration of CTCAE grade 4 toxicity (time to recovery to grade<=3) and of the toxicity overall (time to recovery to grade 0).

Although CTCAE use local laboratories normal ranges to defined grade 0 and grade 1, most protocols for experimental cytototoxic anti-tumor drugs, include eligibility criteria for hematological parameters based on absolute values which do not take into consideration local laboratories normal ranges (e.g. neutrophils count greater than 1.5x10^9/l). The same happens with the re-treatment criteria defined in this type of protocols.

The example in table 5 is based on the assumption that 2.0 10^9/l for the neutrophils count is a safe value with respect to the expected toxicity of the drug on study: the drug was first administered on the 2nd December 2006 (that is day 1), the worst value was observed on day 10 (time to nadir) and recovery above the defined threshold (>2.0 10^9/l) on day 14, four days after the worst value was observed (time to recovery).

Date of Drug Administration (day 0)	Date of Lab Sample	Neutrophils Count Values	Time to Nadir	Time to Recovery
02/12/2006 (day 1)	03/12/2006 (day 2)	2.30		
	05/12/2006 (day 4)	1.90		
	08/12/2006 (day 7)	0.80		
	09/12/2006 (day 8)	0.67		
	10/12/2006 (day 9)	0.48		
	11/12/2006 (day 10)	0.32	10	
	12/12/2006 (day 11)	0.67		
	13/12/2006 (day 12)	1.24		
	14/12/2006 (day 13)	1.89		
	15/12/2006 (day 14)	2.09		4

Table 5: Time to Nadir and Time to Recovery Calculation for Neutrophils Count < 2.0 10^9/l

Figure 9 instead reports the toxic profile for neutrophils count of a drug administered at various dose levels in a phase I study. As it was expected, as the dose level increases the nadir value decreases. What instead is not that different is the data about time to recovery which is very similar (apart for dose level 20) in all the dose levels, confirming that although the toxic effect is more severe it recovers within a similar timeframe.

Dose (mg/m^2)	Nadir/range (neutrophils)	Time to nadir (days/range)	Time to recovery (days/range)
10	2.3 (1 9–2.8)	15 (13–20)	8 (3–15)
15	1.1 (0.4–4.2)	14 (12–20)	7 (1–9)
20	1.0 (0.5–3.7)	14 (7–17)	12 (6–16)
25	0.9 (0.4–2.1)	15 (14–20)	8 (5–13)
27 5	0.5 (0.2–0.9)	8 (7–12)	8 (4–14)

Figure 9: Example of analysis on time to nadir/time to recovery

POSSIBLE DATA ISSUES DURING DATA-ANALYSIS

It may happen at the time of database lock that for whatever reason, although the unit of the local laboratory was provided, the normal range remains missing. In this circumstance, if we don't want to miss useful information, some standard laboratory reference values can be applied. A good set of ranges (for adults) are those provided by the Massachusetts General Hospital[8]; however their application may be not appropriate in some situations, since this references are based on the hospital data and therefore affected by many variables, including the patient population and the laboratory methods used.

TOOLS HELPING THE MANAGEMENT OF LABORATORY DATA

The complexity of the management of lab data, especially when local laboratories are used, requires specific tools (i.e. SAS® macro routines) for supporting all the steps previously described. Regardless of the instruments used, it is recommended to have the following procedures/solutions in place:

- central repository for unit synonyms, where all possible synonyms for laboratory units are collected together with conversion factors to SI units. This repository should be peer reviewed by a team evaluating requests for adding new synonyms;
- a system for automating the conversion from local units to SI units;
- where a system such as the CTCAE is used, establish a process for automatic calculation/conversion from continuous values to categorized values.

CONCLUSIONS

TECHNICAL DATA-MANAGEMENT CONSIDERATIONS

In many studies and especially in early clinical development phase (such as oncology phase I studies), laboratory data constitute 50%-80% of the data to be collected. One possible solution for simplifying the management of laboratory data collected during the course of a clinical trial, is the electronic data transfer from all local laboratories or at least from the investigational sites internal laboratories; however the laboratories selected for electronic data transfer may apply different formats, each one requiring development, maintenance and support, and each receiver or sender in the data chain must work to validate their systems and verify exchanges. A standardization process can improve the electronic data transfer from the local laboratories. For this purpose, the CDISC LAB Team[9] has defined a model for standard representation of laboratory data generated during the conduct of clinical trials. The LAB model is a superset of data fields follows a recognizable and logical hierarchy of clinical laboratory data. The base LAB model can be used to represent all routine "one test, one result" testing, required in clinical hematology, chemistry and urinalysis.

Moreover, with the large quantity of data to be managed, it is also clear that proper systems for supporting the various steps in the laboratory data management together with the support of a specialist in laboratory data management, especially when dealing with multiple laboratory ranges and units, can improve the quality of data to be collected.

STATISTICAL ANALYSIS AND CLINICAL DATA-MANAGEMENT CONSIDERATIONS

When planning data collection and analysis for a trial using different local laboratories the following aspects should be considered to ensure a good proportion between the complexity and associated workload of laboratory data management and analysis and the clinical significance of the results obtained:

- how small are the differences / abnormalities that need to be defined? The answer to this question leads to the choice of a more or less sophisticated method of harmonization of laboratory results (e.g. normalization vs conversion to SI units);
- what is the cost-benefit ratio of collection and management of a large number of normal ranges in the context of oncology studies testing cytotoxic drugs for parameters like WBC, Neutrophils and Platelets, for which the study protocols and the CTCAE toxicity scale define absolute thresholds independent from the laboratory specific normal ranges and where very severe toxicity is expected.

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