ERNDIM
Quantitative Schemes
Cystine in White Blood Cells

ANNUAL REPORT 2019

Scheme Organiser	Scientific Advisor	Website for reporting results	Administration office
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Leeds-Winterswijk, 10 January 2020

1. *Purpose*

The purpose of the ERNDIM External Quality Assurance Scheme for Cystine in White Blood Cells is the monitoring of the analytical quality of the quantitative assay of cystine in white blood cells in the management and diagnosis of patients with cystinosis. For details see www.erndimqa.nl

2. *Participants*

A total of 35 datasets have been submitted.

3. *Design*

The Scheme has been designed, planned and co-ordinated by Daniel Herrera as scientific advisor and Dr. Cas Weykamp as scheme organizer (subcontractor on behalf of SKML), all appointed by and according to the procedure of the ERNDIM Board. The design includes special attention to sample composition and to the layout of the reports. As a subcontractor of ERNDIM, SKML prepare and dispatch EQA samples to the scheme participants and provide a website for on-line submission of results and access to scheme reports.

Samples

The Scheme for Cystine in White Blood Cells consists of 4 different Cystine aliquot and protein pellet pairs that are measured twice a year to ensure duplicate analysis, making 8 sample pairs in total. To prevent that duplicates become predictable, the order of the duplicates are randomised every year. Unfortunately, this year the samples were randomised wrongly. This scheme is a special scheme as it deals with sample pairs of cystine and protein content, therefore the final concentration of cystine related to protein (nmol ½ cystine/mg protein) should remain intact, which was not the case this year. See Table 1 below for an overview of the samples.

Table 1. Pair identification, source and amount of added analytes.

	Samples should have been (target values are depicted):			**Samples were** (target values are depicted):		
Analyte	**Cystine (nmol/aliquot)**	**Protein (mg/pellet)**	**Cystine (nmol 1/2 cys/mg protein)**	**Cystine (nmol/aliquot)**	**Protein (mg/pellet)**	**Cystine (nmol 1/2 cys/mg protein)**
Source	Sigma 49603	Instruch. 11930	-	Sigma 49603	Instruch. 11930	-
2019.01	0.2	0.35	1.14	0.2	0.2	2.00
2019.02	2	1.3	3.08	2	1.3	3.08
2019.03	0.05	0.2	0.50	0.05	0.35	0.29
2019.04	0.55	0.6	1.83	0.55	0.6	1.83
2019.05	0.05	0.2	0.50	0.05	0.35	0.29
2019.06	2	1.3	3.08	2	0.6	6.67
2019.07	0.55	0.6	1.83	0.55	0.2	5.50
2019.08	0.2	0.35	1.14	0.2	1.3	0.31
	Sample pairs: 2019.01-08; 2019.02-06; 2019.03-05; 2019.04-07			No sample pairs for Cystine per Protein, and pairs for Cystine and Protein are not identical		

Reports

All data-transfer, the submission of data as well as request and viewing of reports proceeded via the interactive website www.erndimqa.nl The results of your laboratory are confidential and only accessible to you (with your name and password). The anonymised mean results of all labs are accessible to all participants. Statistics of the respective reports are explained in the general information section of the website.

Unfortunately, the software cannot be adjusted to re-match the missing pairs that arose due to the incorrect randomising of samples as discussed above. As a result there are no duplicates for Cystine (nmol ½ cystine/mg protein) in the website calculations to evaluate. Therefore the Annual report on the website is switched off and shows no results. The calculations were performed offline of the website, meaning that the Annual Report cannot be displayed on the website but is sent to the individual participants by email. There are no consequences for the yearly Certificate; results as presented in the Annual Report are also shown at your certificate.
For the Analyte in Detail report duplicates are not essential and participants have been able to evaluate their results against their peers throughout the year.

An important characteristic of the website is that it supplies short-term and long-term reports.
Short-term reports on the eight individual specimens are available two weeks after the submission deadline and provide up-to-date information on analytical performance. Although technically reports could be immediately available a delay time of 14 days has been introduced to enable the scientific advisor to inspect the results and add his comment to the report.
The **annual long-term report** summarises the results of the whole year.

A second important characteristic of the ERNDIM website is the different levels of detail of results which allows individual laboratories the choice of fully detailed and/or summarised reports.

The “Analyte in Detail” is the most detailed report and shows results of a specific analyte in a specific sample.
A more condensed report is the “Current Report” which summarises the performance of all analytes in a specific sample.
The Annual Report summarizes all results giving an indication of overall performance for all analytes in all 8 samples.
Depending on the responsibilities within the laboratory participants can choose to inspect the annual report (QC managers) or all (or part of) detailed reports (scientific staff).

4. Discussion of Results in the Annual Report 2019

In this part the results as seen in the annual report 2019 will be discussed. Please print out your annual report from the website when you follow the various aspects below and keep in mind that we only discuss the results of “all labs”. It is up to you to inspect and interpret the results of your own laboratory.

4.1 Accuracy

A first approach to evaluating your performance in terms of accuracy is comparison of your mean values in the eight samples with those of all labs. This is shown in the columns "your lab" and "all labs" under the heading "Accuracy”. For example for protein the mean of all labs is 0.598 mg/vial, with which you can compare the mean of your lab.

4.2 Recovery

A second approach to describe accuracy is the percentage recovery of added analyte. In this approach the amounts of weighed quantities added to the samples are the assumed target values after adjustment for blank values. The correlation between weighed amounts (on the x-axis) and your measured quantities (on the y-axis) has been calculated. The slope of the resulting relationship (“a” in y = ax + b) in this formula multiplied by 100% is your recovery of the added amounts. The outcome for your lab in comparison to the median outcome of all labs is shown in the column “Recovery”.
It can be seen that the mean recovery of cystine (nmol/aliquot) is 96% and of protein is 94%, which is reassuring. We are all measuring the same thing.

4.3 Precision

Reproducibility is an important parameter for the analytical performance of a laboratory and is addressed in the schemes’ design. Samples provided in pairs can be regarded as duplicates from which CV’s can be calculated. The column “Precision” in the annual report shows your CV’s in comparison to the mean value for all labs. The mean CV for protein is 7.5% and for cystine (nmol/aliquot) is 13.7%.

4.4 Linearity

Linearity over the whole relevant analytical range is another important parameter for analytical quality and is also examined within the schemes. A comparison of the weighed quantities on the x-axis and your measured quantities on the y-axis allows calculation of the coefficient of regression (**r**). The column “Linearity” in the annual report shows your **r** values in comparison to the median **r** values for all labs. Ideally the **r** value is close to 1.000 and this is indeed observed with a value of 0.993 for Cystine (nmol/aliquot) and 0.995 for Protein.

4.5 Interlab CV

For comparison for diagnosis and monitoring of treatment for one patient in different hospitals and for use of shared reference values it is essential to have a high degree of harmonization between results of laboratories. Part of the schemes' design is to monitor this by calculating the Interlaboratory CV. This, along with the number of laboratories who submitted results is shown in the column "Data all labs" in the annual report. We see an interlab CV of 13.4% for protein, 23.3% for cystine (nmol/aliquot) and of 29.5% for cystine (nmol ½ cys/mg protein).

4.6 Interrelationships between results

Cystine (nmol ½ cys/mg protein) is a ratio of the assays of cystine (nmol/aliquot) and protein (mg/pellet). The precision will be the cumulated precision of both assays.

4.7 Report in correct numbers

As we have indicated in previous reports it is important to report in the correct units. Although we feel that nearly all labs do that now, some strange results of individual labs might be traced back to "clerical errors". So if you have a deviating result, please check if you reported your result in the correct units.

4.8 Your performance: Flags

In order to easily judge performance of individual laboratories the annual report of an individual laboratory may include flags (different colours starting from this year) in case of poor performance for accuracy, precision, linearity and recovery. Analytes with satisfactory performance for at least three of the four parameters (thus no or only one flag) receive a green flag. Thus a green flag indicates satisfactory performance for analysis of that particular analyte. Criteria for flags can be found in the general information on the website (on this website under general information; interactive website, explanation annual report).

4.9 Poor Performance Policy

A wide dispersion in the overall performance of individual laboratories is evident. Table 2 shows the percentage of flags observed. 58% of the laboratories have no flag at all and thus have attained excellent overall performance. In contrast, at the other extreme there are also 6% of laboratories with more than 25% flags. Following intensive discussion within the ERNDIM board and Scientific Advisory Board (SAB) and taking into account feedback from participants we have been able to agree on a harmonised scoring system for the various branches of the Diagnostic Proficiency schemes and qualitative schemes. We have also tested a scoring system for the quantitative schemes as described in our Newsletter of Spring 2009. In parallel to this the SAB has agreed levels of adequate performance for all the schemes and these will be re-evaluated annually. The scoring systems have been carefully evaluated by members of the SAB and have been applied to assess performance in our schemes from 2007 onwards. The ERNDIM Board has decided that the Scientific Advisor will judge the performance of the individual laboratories based on these levels of satisfactory performance and issue a letter of advice of failure to achieve satisfactory performance to those laboratories which do not achieve satisfactory performance. The letter is intended to instigate dialogue between the EQA scheme organiser and the participating laboratory in order to solve any particular analytical problems and to improve quality of performance of labs in the pursuit of our overall aim to improve quality of diagnostic services in this field.

Table 2. Percentage Flags

% Red Flags seen in Annual Report	Percentage Labs In this Category	Cumulative Percentage Of Labs
>25%	6%	6%
25%	6%	12%
20 – 25%	0%	12%
15 – 20%	15%	27%
10 – 15%	0%	27%
5 – 10%	15%	42%
0 – 5%	0%	42%
0%	58%	100%

4.10 Certificates

As for other schemes the performance as it is indicated by the red/green flags in the individual laboratories annual report is summarised in the new style of annual participation certificate. The certificate lists the total number of analytes in the scheme, the number for which results have been submitted and the number for which satisfactory performance has been achieved. It is important to bear in mind that the certificate has to be backed up by the individual annual report in the case of internal or external auditing.

4.11 Additional Specific Remarks of the Scientific Advisor

There are laboratories having outlier results, some of them with two or more outliers what it makes difficult the assessment of the analytical performance of those laboratories. Some of those outlier results may be explained by simple calculating errors; however it is not always the case what it is of clinical concern.
In 2020 the scheme will pilot the introduction of clinical information and interpretation of the results. We hope this will help to assess better those laboratories with aberrant results.

5. *Summary*

We feel that the scheme is well-established now. The mean performance of the labs, especially the recovery of added cystine and protein, is satisfactory but of course the performance of some individual labs requires improvement. The elevated Interlab CVs demonstrates lack of standardization which requires improvement. We would like to emphasize the need for all laboratories to use internal quality control. At its simplest this can be made from pooling surplus supernatants from assayed samples. We think that some of the aberrant results are still caused by simple calculating errors.

6. *Preview of the Scheme in 2020*

The design of the 2020-scheme is in principle the same as in 2019; however the scheme will pilot the introduction of clinical details and interpretation of the results for each of the distributions. The clinical scenarios and concentrations of cystine (nmol ½ cystine/mg protein) are similar to real cases reported in the literature and/or diagnosed in clinical laboratories. The interpretation options will be different for each of the distributions (usually three or four options) and we will be requesting information about how your laboratory would comment on the report in a similar case. There is an educational component in this modified scheme and the results, interpretation and the information provided by the laboratories will be summarized in the annual report. The interpretation component of the scheme will not be scored in 2020. If the new design adds value to the scheme, it will be fully implemented in 2021 and the interpretation component will be scored and reflected in your yearly certificate.

7. Questions, Comments and Suggestions

If you have any questions, comments or suggestions please address to the scientific advisor of the Scheme Mr. D. Herrera (daniel.herrera@nhs.net) or the scheme organiser Dr. Cas Weykamp (c.w.weykamp@skbwinterswijk.nl).

Leeds, 10 January 2020

Mr Daniel Juan Herrera
Scientific Advisor

Please note:
This annual report is intended for participants of the ERNDIM Cystine in White Blood Cells scheme. The contents should not be used for any publication without permission of the scheme advisor.

The fact that your laboratory participates in ERNDIM schemes is not confidential. However, the raw data and performance scores are confidential and will be shared within ERNDIM for the purpose of evaluating your laboratory performance, unless ERNDIM is required to disclose performance data by a relevant government agency. For details, please see the terms and conditions in the ERNDIM Privacy Policy on www.erndim.org.