ERNDIM Quantitative Schemes Neurotransmitters in CSF

ANNUAL REPORT 2025

Scheme Organiser	Scientific Advisors	Website for reporting results	Administration office
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1. *Purpose*

The purpose of the ERNDIM External Quality Assurance Scheme for Neurotransmitters is the monitoring of the analytical quality and interpretation of the quantitative assay of neurotransmitters in CSF in laboratories involved in the screening and diagnosis of patients with inherited metabolic disorders. For details see www.erndim.org / www.ERNDIMQA.nl

2. *Participants*

A total of 35 datasets were submitted and 1 laboratory did not submit enough results to generate an annual report.

3. *Design*

The Scheme has been designed, planned, and coordinated by Dr. Simon Pope and Prof. Simon Heales as scientific advisors and Dr. R.M. Schoeman as scheme organiser (on behalf of the MCA Laboratory), each appointed by and according to the procedures of the ERNDIM Board. The design includes samples and reports which are connected to provide information with a balance between short-term and long-term reports and between detailed and aggregated information. As a subcontractor of ERNDIM, the MCA Laboratory prepares and distributes EQA samples to the scheme participants and provide a website for on-line submission of results and access to scheme reports.

Samples

The scheme consisted of 8 lyophilised samples consisting of an artificial matrix spiked with various amounts of the respective analytes. The samples were identical two by two: the pairs, analytes and their source as well as the added amounts are in Table 1 below. Samples have been tested for stability and homogeneity according to ISO 13528, and are stable for the duration of the scheme's submission calendar when stored under defined conditions.

[1] If this Annual Report is not Version 1 for this scheme year, go to APPENDIX 1 for details of the changes made since the last version of this document

Table 1. Samples

Analyte	Source	Spiked Quantities in nmol/liter			
		Sample Pair 2025. 01-08	**Sample Pair 2025. 02-07**	**Sample Pair 2025. 03-06**	**Sample Pair 2025. 04-05**
3-methyl dopa	Sigma M4255	8.0	15.0	25.0	125
5-methyltetra-hydrofolic acid	Merck 1379081	72.0	100	50.0	5.0
5-HIAA	Sigma H8876	73.0	80.0	31.0	358
Biopterin	Schircks Laboratories 11.203	15.0	20.0	25.0	45.0
5-OH-Tryptophan	Sigma H9772	5.0	10.0	4.0	25.0
Homovanillic acid	Sigma H1252	10.0	207	165	713
HVA:5HIAA ratio	Not applicable	0.1	2.6	5.3	2.0
Neopterin	Schircks Laboratories 11.303	15.0	20.0	40.0	20.0

Reports

All data-transfer, the submission of data as well as request and viewing of reports proceeded via the interactive website www.erndimqa.nl which can also be reached through the ERNDIM website (www.erndim.org). 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.

An important characteristic of the website is that it supplies short-term and long-term reports. **Short-term reports** are associated with the eight individual specimens, for each of which there has been a specific deadline in the year 2025. Three weeks after the respective deadlines, participants could request their reports and as such had eight times up-to-date information on their analytical performance. Although it is technically possible to produce reports immediately, there is a delay of 21 days to enable the scientific advisor to inspect the results and add comments to the report when appropriate.
The **annual long-term report** is based on the design-anchored connection between samples which enables a range of analytical parameters (accuracy, precision, linearity, recovery and inter-lab dispersion) to be reported once the annual cycle has been completed.

A second important characteristic of the website is the wide range in aggregation of results which permits labs to make an individual choice for detailed and/or aggregated reports. The most detailed report which can be requested from the website is the "Analyte in Detail" which shows results of a specific analyte in a specific sample (64 such Analyte-in-Detail-reports can be requested in the year 2025 cycle). A more condensed report is the "Current Report" which summarizes the performance of all analytes in a specific sample (8 such Current Reports can be requested in 2025). The highest degree of aggregation has the Annual Report which summarizes the performance of all analytes of all 8 samples (1 such Annual-Report can be requested

in 2025). Depending on their position in the laboratory one can choose to have a glance at only the annual report (managers) or at all 64 detailed reports (technicians)…..

4. *Discussion of Results in the Annual Report 2025*

In this section, the results of the Annual Report 2025 are summarised in terms of accuracy, precision, linearity, recovery, inter-laboratory co-efficient of variation (CV) and relations between these parameters. Please keep at hand your annual report from the Interactive Website when you read the “guided tour” below and keep in mind that we only discuss the results of “all labs”: it is up to you to inspect and interpret the specific results of your laboratory.

4.1. *Accuracy*

A first approach to describe the accuracy is comparison of your mean outcome in the eight samples with the mean of all labs. This is shown in the columns "your lab" and "all labs" under the heading "Accuracy", respectively. For 3-methyl dopa the mean of all labs is 40.3 nmol/L with which you can compare the mean of your lab.

It is important to recognise that using ERNDIM EQA material to establish bias is potentially a limitation. The bias of the method has been determined by comparing results to a derivation of the ERNDIM all laboratory trimmed mean, not a true target value. As the materials produced by the scheme are not reference materials, the bias determined is not a measure of absolute accuracy and is simply a measure of performance relative to other laboratories.

4.2. *Precision*

Reproducibility is an important parameter for quality in the laboratory and is encountered in the schemes’ design. Samples come in pairs which can be regarded as duplicates from which CV’s can be calculated (Intra Laboratory CV as indicator for reproducibility). Outcome for your lab in comparison to the median of all labs is shown in the column “Precision” of the Annual Report. Precision ranges from 3.9% for HVA to 11.3% for Biopterin. The overall intra-lab CV is 8.2%.

4.3. *Recovery*

A second approach to describe accuracy is the percentage recovery of added analyte. In this approach it is assumed that the recovery of the weighed quantities is the target value. The correlation between weighed quantities as added to the samples (on the x-axis) and your measured quantities (on the y-axis) has been calculated. The slope of the correlation multiplied by 100% is your recovery of the added amounts. The recovery ranges from 72% for Biopterin to 105% for 5MTHF. The overall recovery is 91%.

4.4. *Linearity*

Linearity over the whole relevant analytical range is another important parameter for analytical quality. Again, this is encountered in the schemes’ design. With weighed quantities on the x-axis and your measured quantities on the y-axis the coefficient of regression (r) has been calculated. Outcome for your lab in comparison to the median of all labs is in the column “Linearity” of the annual report. It can be seen that the coefficient of regression ranges from 0.951 for HVA:5HIAA ratio to 0.999 for HVA.

4.5. *Interlab CV*

For comparison of outcome for one patient in different hospitals and for use of shared reference values it is relevant to have a high degree of harmonization between results of various 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. It can be seen that most laboratories submitted results for 5HIAA (n=33) whereas only 25 labs assayed 5-MTHF and Neopterin. The Interlab CV ranges from 10.9% for HVA to 27.8% for 5-MTHF. The mean Interlab CV for all analytes is 20.5%.

4.6. *Cross Sectional Relations*

The various parameters as described above often have an interrelation: often more than one parameter directs towards good or bad analytical control.
This pattern, clearly seen in the other ERNDIM schemes is less prominent in the Neurotransmitter scheme.

4.7. *Your performance: red and green flags*

After some years of discussion and planning a system to judge performance of individual laboratories is implemented starting from January 2009. In the annual report of an individual laboratory flags indicate 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 or no result) receive a green flag. Thus, a green flag indicates satisfactory performance for analysis of that particular analyte while a red flag indicates that your laboratory has failed to attain satisfactory performance. Criteria for flags can be found in the general information on the website (general information; interactive website, explanation annual report).

4.8. *Poor Performance Policy*

A wide dispersion in the overall performance of individual laboratories is evident. Table 2 shows the percentage of flags observed. 38% 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. In parallel to this the SAB has agreed levels of adequate performance for all the schemes and these will be re-evaluated annually. For further information, please refer to the Framework for Assessment and Education for Hybrid Schemes on our website (https://eqa.erndim.org/information/view/14). 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 in order to improve quality of performance of labs in the pursuit of our overall aim to improve quality of diagnostic services in this field.

If your laboratory is assigned poor performance and you wish to appeal against this classification, please email the ERNDIM Administration Office (admin@erndim.org), with full details of the reason for your appeal, within one month receiving your Performance Support Letter. Details of how to appeal poor performance are included in the Performance Support Letter sent to poor performing laboratories.

Table 2. Percentage Flags

% Red Flags seen in Annual Report	Percentage Labs In this Category	Cumulative Percentage Of Labs
>25%	6%	6%
25%	9%	15%
>20 – 25%	3%	18%
>15 – 20%	3%	21%
>10 – 15%	6%	27%
>5 – 10%	26%	53%
>0 – 5%	9%	62%
0%	38%	100%

4.9. *Interpretation*

In this scheme we also requested the interpretation of test results. Table 3 shows the interpretation frequency for the respective sample pairs. The correct interpretation is marked with a green box. It can be seen that interpretation is nearly always correct.

Table 3.

Description	Pair 2025. 01-08 (14y-10y)	Pair 2025. 02-07 (6y-16y)	Pair 2025. 03-06 (3y-4y)	Pair 2025. 04-05 (2Mo-4y)
No obvious disorder of serotonin or dopamine metabolism	2 – 1	27 – 31	8 - 13	8 – 4
A patient with a folate deficiency	0 – 0	0 – 0	5 - 5	23 – 25
A patient with isolated impaired serotonin turnover	0 - 0	0 – 0	9 – 10	1 – 0
A patient with tyrosine hydroxylase deficiency, not on treatment	28 – 31	3 – 0	0 – 0	0 – 0
A patient with a pterin disorder on treatment	1 – 0	0 – 0	9 – 3	0 – 1

To prevent laboratories from deriving the duplicate samples from the age of the patients, ages of samples for non-duplicates were the same as duplicates (Example: Samples 5 and 6 were given the same ages).

4.10 Certificates

Neurotransmitters are included in the certificates. The certificates now include separate scoring for quantitation and interpretation.

4.11 Additional Specific Remarks of the Scientific Advisor

Neopterin and biopterin were included in the scheme for the first time in 2025. 25 laboratories measured neopterin and 23 measured biopterin. The CVs for these two new analytes were comparable to the other analytes in the scheme – around 10% precision on duplicates and around 20% for the interlab CV.

5. *Summary*

The number of participants in the scheme has settled in the last few years to around 35. Results have shown a good degree of consistency between the laboratories around the world.

The interpretive part is included to see how different laboratories, with different CSF collection protocols/fractions, reference ranges and populations, interpret the results. We believe the interpretation is very important and we try to make the samples so that they reflect actual patient samples we have seen in the laboratory. We would encourage all participants to choose an interpretive comment and regularly review their results versus the other participants.
A brief discussion of each of the duplicate samples is given below.

Samples 01-08 – This sample had low HVA and HVA:5HIAA ratio, suggestive of a tyrosine hydroxylase deficiency.

Samples 02-07 – This sample had all the analytes within the age-related reference ranges, consistent with no obvious disorder of serotonin or dopamine metabolism.

Samples 03-06 – This sample caused some confusion. It was originally designed to reflect a patient with isolated impaired serotonin turnover. However, the median results for all labs showed borderline low 5HIAA **and** 5MTHF, so the scoring was adjusted to reflect these borderline results and not unnecessarily penalize labs.

Samples 04-05 – This sample had very low 5MTHF, consistent with a patient with folate deficiency. Since not all labs measured 5MTHF, the scoring for sample 5 was changed to not penalize labs who did not measure this analyte.

The interpretive scoring for the scheme was good with the majority of labs scoring 10 or above.

6. *Preview Scheme 2026*

A scoring system has been agreed for hybrid schemes. 2 points will be awarded for a correct answer and 0 for an incorrect answer. Occasionally, where a participant is partially correct a score of 1 point will be given. At the end of the year, a final score out of 16 (2 points x 8 submissions) will be calculated. A score of 10/16 or above, with no critical errors, will be required for performance to be considered satisfactory.

7. *Questions, Suggestions and Complaints*

If you have any questions, remarks or suggestions please address to the scientific advisors or the scheme organiser Dr. R.M. Schoeman (mca.office@skbwinterswijk.nl).

Most complaints received by ERNDIM consist of minor misunderstandings or problems with samples, which can usually be resolved via direct contact with the ERNDIM administrative staff. If you wish to file a formal complaint, please email your complaint with details of your issue to admin@erndim.org or contact us through our website at https://www.erndim.org/contact-us/

London, 2nd February 2025

Simon Heales Simon Pope

Scientific Advisors

Please note:
This annual report is intended for participants of the ERNDIM CSF Neurotransmitters 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.

APPENDIX 1. Change log (changes since the last version)

Version Number	Published	Amendments
1	5th February 2026	• 2025 annual report published
2	10th February 2026	• Error in Administration Office address. Address updated.

END