Research Protocol - Evaluation of the Nova StatSensor Xpress Creatinine Point-Of-Care Handheld Analyzer

Evaluation point-of-care handheld analyzer Nova StatSensor® iXpress™ Creatinine (Nova Biomedical Cooperation, Waltham, MA, USA)

Study protocol

MSF International, Amsterdam, Netherlands
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Sint Lucas Andreas Ziekenhuis, Amsterdam, Netherlands

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Study	Evaluation point-of-care handheld analyzer Nova StatSensor® Xpress™ Creatinine (Nova Biomedical Cooperation, Waltham, MA, USA)		
Collaboration	University Medical Centre, Utrecht, Netherlands		
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Development study protocol	Cara Kosack		MSF
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1. Background

Creatinin is a parameter that is required to monitor renal function. This parameter is important to follow in patients under treatment with potentially toxic renal drugs, such as the anti-HIV drug Tenofavir.

Médecins Sans Frontières (MSF), a humanitarian medical emergency relief organization, operates in resource-limited and often decentralized settings where no laboratory is available to carry out blood analysis.
In large HIV projects potentially toxic renal drugs are in use leading to the demand for point-of-care analyzers for appropriate patient management in resource-limited settings.

The StatSensor® iXpress™ Creatinine (catalogue number 48635) from Nova (Nova Biomedical Cooperation, Waltham, MA, USA) is a hand held Creatinine analyzer for the quantitative measurement of creatinine in capillary, venous, and arterial whole blood.
We have chosen to evaluate the performance of this point-of-care analyzer as it can operate at a temperature of 15-40 °C and at a relative humidity level of 10-90%, which makes it potentially suitable for typical MSF settings in Africa and other parts of the world
The required sample volume of the StatSensor® iXpress™ Creatinine is 1.2 µl and the measurements range is 0.30 to 12.0 mg/dL or 27 to 1056 µmol/L.

To date evaluations of the point-of-care analyzer have been showing varying results.[1-3]

In addition, the stability of creatinine in serum is well established[4], but there is no data on its stability in whole blood. Li-Heparin anti-coagulated blood will be used in this evaluation and could be used in the field in some settings, and it is important to know whether creatinine is stable in these conditions to assess if the measurement can be delayed or not.

2. Study hypothesis and objective

Study hypothesis
Nova StatSensor® Xpress™ Creatinine has sufficient precision (i.e. coefficient of variation [CV] <10%) and sufficient accuracy when compared to a reference method (i.e. bias <10% and limits of agreement) to be used for patient monitoring in settings with no access to laboratory.

Objective
To evaluate the precision and accuracy of the Nova StatSensor® Xpress™ Creatinine when compared to the reference method (Ortho Vitros)) at Sint Lucas Andreas Ziekenhuis (SLAZ), Amsterdam, the Netherlands.

Secondary objective
To measure the stability of creatinine in Li-Heparin anticoagulated blood/

3. Methods

Study design
This is a quantitative diagnostic test precision and accuracy evaluation of Nova StatSensor® Xpress™ Creatinine.

Sample size

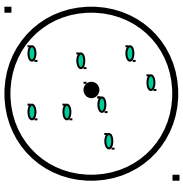
Stability
One blood sample with high Creatinin level (i.e. > 2 mg/dl) will be measured 5 times at all 3 Nova StatSensor® Xpress™ Creatinine analyzers at 30 minutes after venous puncture.
At time points 60, 90, 120, 150, 180, 210 and 240 minutes after venous puncture the measurements will eb performed on all three machines in duplicate.
= (5 tests * 3 machines * 1 time point) + (2 tests * 3 machines * 7 time points) = 15 + 42 = 57 tests

If all measurements have a CV of less than <5% for all time points, the precision and accuracy testing will be performed.

Precision (repeatability)
The second step of this evaluation will be the assessment of precision of three different analyzers.

For this evaluation, three different blood specimens will be selected that will correspond to:

- 3 * normal values (Creatinine <1.3 mg/dl)
- 3 * low pathological values (Creatinine 1.3-3 mg/dl)
- 3 * high pathological values (Creatinine >3 mg/dl)

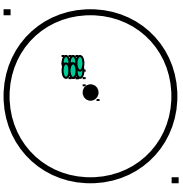


Each specimen will be measured 8 times on each of three analyzers to assess for inter machine variation.
= 9 specimens * 8 measurements * 3 machines = 216 tests

Note: The repeated measurements on each analyzer should be done as quickly as possible, i.e. within a maximum of 20 minutes for each analyzer (maximum of 1 hour for all three analyzers with one specimen).

Accuracy
For the evaluation of the accuracy (maximum acceptable variation from reference standard <10% with an acceptable correlation coefficient is > 95 %):

- 20 samples with normal values (Creatinine <1.3 mg/dl)
- 20 samples with low pathological values (Creatinine 1.3-3 mg/dl)
- 20 samples with high pathological values Creatinine >3 mg/dl)



Measurements will be repeated on two different analyzers to assess for inter machine variation.
= 80 samples * 2 machines = 160 tests

Total number of tests: stability 57 + precision 216 + accuracy 160 = 433

We need to be more specific on volume of blood required and additional blood drawing.

Reference standard tests
Creatinin measurements by the Ortho Vitros analyzer using the xyz method will function as reference standard. Measurements will be carried out in duplicate and the mean will eb calculated.

Data entry
Following information will be entered in an excel file.

1. ID number
2. Date of birth
3. Gender
4. Result of reference standard test (i.e. mean of two measurements)
5. Results of Nova StatSensor® Xpress™ Creatinine for stability testing, precision and accuracy testing

Analysis

Stability
The duplicate measurements and mean value will be plotted on a graph with time on the x axis and creatinine measurement on the y axis. Another graph will show plot the percentage of initial mean value (i.e. at 30 minutes) at different time points, in order to detect a potential decay with time.
For each specimen, the mean, standard deviation and coefficient of variation will be calculated using all time points if no obvious decay is detected, or including the time points in a restricted time range if an effect of time is detected (visually).
We will conclude that the blood collected in Li-Heparin is stable for a certain duration of time if the CV of all time points during this duration are within the precision calculated above.

Precision
For each specimen and each analyser, the mean, standard deviation and coefficient of variation (i.e. SD / mean) will be calculated.
Results will be considered very good if all 3 specimens show CV <3 %, good if all CV <5 % and acceptable if all CV <10 %.

Accuracy

The results of the Nova StatSensor® Xpress™ Creatinine evaluation will be compared to the reference standard using Bland-Altman analysis:

- Bias: mean of the difference
- Limits of agreement: bias +/- (1.96*standard deviation)

The Bland Altman analysis will be applied:

- To compare the repeated testing on 2 different Nova StatSensor® Xpress™ Creatinine analysers. The coefficient of reproducibility will be calculated
- To compare the mean of the values obtained with the 2 analyzers with the value of the reference method (accuracy). The bias will be obtained from this analysis, and the limits of agreement (and 95% CI) will be corrected to take into account the use of the mean, instead of individual measurements.

The bias will be considered good if < 0.1 mg/dl, acceptable if < 0.3 mg/dl.
The limits of agreement will be considered good if < +/- 0.3 mg/dl, acceptable if < 0.5 mg/dl.

In addition, the measurements on the analyser vs. reference method will be plotted on a correlation graph and the Pearson correlation coefficient will be calculated.

All analysis will be carried out using STATA version 11 (StataCorp, College Station, Texas, USA).

4. Collaboration

The clinical chemistry laboratory at the Sint Lucas Andres Hospital (SLAZ), Amsterdam, Netherlands is MSF's and Epicentre's counterpart.
MSF will provide the SLAZ with the following materials:

- Nova StatSensor® Xpress™ Creatinine analyzers
- Nova StatSensor® Xpress™ Creatinine test strips
- Nova StatSensor® Xpress™ Creatinine control solutions Level 1-3
- Nova StatSensor® Xpress™ Creatinine linearity solutions, level 1-5

Employees or students of the SLAZ clinical chemistry laboratory will carry out the evaluation of the Nova StatSensor® Xpress™ Creatinine analyzer.

MSF and Epicentre will carry out the analysis of the data.

5. Formal and ethical approval

The study will be submitted to SLAZ ethical review board and only be carried out after their approval. The study will be carried out in accordance with the Declaration of Helsinki concerning medical research in humans.

6. Financing the study

MSF will purchase the required Nova StatSensor® Xpress™ Creatinine analyzers, test strips, control and linearity solutions.
The SLAZ will provide the results of the reference standard measurements and provide human resources to carry out the measurements on the Nova StatSensor® Xpress™ Creatinine and report the results.

7. References

1. Shephard M, Peake M, Corso O, Shephard A, Mazzachi B, Spaeth B, Barbara J, Mathew T. Assessment of the Nova StatSensor whole blood point-of-care creatinine analyzer for the measurement of kidney function in screening for chronic kidney disease. Clin Chem Lab Med. 2010 Aug;48(8):1113-9.

2. Schnabl KL, Bagherpoor S, Diker P, Cursio C, Dubois J, Yip PM. Evaluation of the analytical performance of the Nova StatSensor creatinine meter and reagent strip technology for whole blood testing. Clin Biochem. 2010 Aug;43(12):1026-9. Epub 2010 Apr 21.

3. Straseski JA, Lyon ME, Clarke W, Dubois JA, Phelan LA, Lyon AW. Investigating interferences of a whole-blood point-of-care creatinine analyzer: comparison to plasma enzymatic and definitive creatinine methods in an acute-care setting. Clin Chem. 2011 Nov;57(11):1566-73. doi: 10.1373/clinchem.2011.165480. Epub 2011 Sep 15.

4. Thomas L. Labor und Diagnose. 5. Auflage . Dade Behring. Page 380

Annex 1: Order list MSF

Name article	**Catalogue number**	**Quantity to be ordered**	**Price per unit**	**Price total**
Nova StatSensor® Xpress-i™ Creatinine	48635	3	€ 300 (excl. VAT)	€ 900 (excl. VAT)
Nova StatSensor® Xpress™ Creatinine Strips (2x 25 strips)	43272	Stability testing: 57 Precision: 216 Accuracy: 160 **Total: 500 single tests** **(= 10 packs of 50)**	€ 180 (excl. VAT)	€ 1.800 (excl. VAT)
Creatinine Linearity solutions, Level 1-5	46950	1	64,00	64,00
Creatinine Control solutions, Level 1	43921	1	6,75	6,75
Creatinine Control solutions, Level 2	43922	1	6,75	6,75
Creatinine Control solutions, Level 3	43923	1	6,75	6,75
Total				**€ 2784,25 (excl .VAT)**