Traceability and Measurement Uncertainty within Clinical Biochemistry

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Relevant Staff Groups to which document applies | All staff within Clinical Biochemistry and Immunology
Copy No | 1

Relevant safety data, COSHH and risk assessments:

Mark relevant procedures/policies

<table>
<thead>
<tr>
<th>VDU</th>
<th>Lifting/Handling</th>
<th>COSHH</th>
<th>Spillage</th>
<th>Disposal</th>
<th>Sharps</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

The above risk/safety assessments must be read and understood before carrying out this procedure. Details are recorded in the main text of the document.

Additional Standard cross references:

Standard ..............................................
Traceability and Measurement Uncertainty within Clinical Biochemistry

Traceability
Traceability is defined as the property of the result of a measurement or the value of a standard whereby it can be related back to stated references which are usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties.

For the quantitative assays performed within Clinical Biochemistry, calibrators traceable to national or international standards are used where possible. The CE marked kits and calibrators used within this laboratory contain the information regarding the traceability to reference materials within the kits. This laboratory does not produce any of its own calibrators. Calibrator information is detailed within the Standard Operating Procedure for each assay and these should be referred to for further information.

For the qualitative assays used within Clinical Biochemistry such as pregnancy testing, these kits are CE marked and performance is assessed via External Quality Assessment participation. The assays used for qualitative analysis are not calibrated but do have an internal quality control check which ensures the quality of the product and result produced.

Uncertainty of results
Measurement uncertainty (MU) is defined as a parameter, associated with the result of measurement that characterises the dispersion of the values that could reasonably be attributed to the measurand. By quantifying the possible spread of measurements an estimate of the confidence in the result may be obtained. Measurement uncertainties can come from the measuring instrument, from the item being measured, from the environment, from the operator, and from other sources. When the uncertainty in a measurement is evaluated and stated, the fitness for purpose of the measurement can be properly judged.

Identifying and reducing uncertainty
Within Clinical Biochemistry sources of uncertainty can be categorised into the following three areas; Pre examination, Examination and Post examination

The laboratory undertakes many procedures to ensure where possible uncertainty is minimised or at least accounted for. The following information details how this is achieved within CDDFT.
## Pre Examination

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>CDDFT method of identification and minimisation</th>
<th>Associated documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient state eg: fasting Patient preparation Time of sample collection</td>
<td>Patient Information Leaflets for specific tests Pathology Handbook on Trust intranet for specimen requirements and preparation conditions Biochemistry and Immunology laboratory and clinical contacts on the intranet/internet Referred work database and folders within the laboratory.</td>
<td>Patient information leaflets are available on Q-Pulse. Referred work database maintained by Senior BMS staff and Clinical Scientists.</td>
</tr>
<tr>
<td>Collection method</td>
<td>Information regarding the collection of samples can be found in the Pathology Handbook on the Trust intranet. The laboratory has also published advice on how samples should be taken.</td>
<td>Refer to Pathology Handbook on Trust Intranet.</td>
</tr>
<tr>
<td>Sample transport</td>
<td>All samples should be sealed within the plastic bag that accompanies the request card (except 24 hour urine bottles) Guidance is provided in the Pathology Handbook regarding allowable time frame for sample delivery to laboratory (this is assay dependent).</td>
<td>Refer to Pathology Handbook on Trust Intranet.</td>
</tr>
<tr>
<td>Receipt of samples into CDDFT laboratories</td>
<td>Staff training completed and SOP followed.</td>
<td>Refer to SOP LP/PA/GR001 – Receipt of sample and to LP/PA/IM/SOP33 – Specimen Reception – Immunology</td>
</tr>
<tr>
<td>Samples requiring referral to other laboratories</td>
<td>Information regarding the referral of samples to other laboratories can be found in associated SOP. Database maintained by Senior BMS/Clinical Scientists Referral labs EQA, UKAS and turnaround information recorded</td>
<td>Refer to SOP LP/PA/GR063 - Referral Procedure - Biochemistry. Refer to QF/PA/IM/HB1 – Immunology Referral Test list</td>
</tr>
<tr>
<td>Sample storage</td>
<td>All staff follow the requirements set out in the relevant assay SOPs. Referred work database and</td>
<td>Refer to LP/PA/CB/OP97 – Biochemistry control of process and quality records and clinical material</td>
</tr>
<tr>
<td>Examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sources of uncertainty</td>
<td>CDDFT method of identification and minimisation</td>
<td>Associated documentation</td>
</tr>
</tbody>
</table>
| Analytical equipment | • All instruments and kits are procured following the Trust procurement policy.  
• All instruments and kits are used according to manufacturers’ instructions. | • Refer to individual SOPs for instruments and assays on QPulse.  
• Refer to LP/PA/CB/OP123 - Management of materials and Stock control, Quality control, Calibrators, reagents, and LP/PA/IM/SOP13 - Monitoring stock and Receiving/Receipting Goods for Immunology section. |
| Reagents | • All assays within Clinical Biochemistry and Immunology are CE marked.  
• All assays have SOPs written detailing reagent use.  
• All reagents are dated with an in use date and checked visually to ensure they are in good condition before they are used.  
• Reagents are stored according to the manufacturers’ guidelines. | |
| Calibration | • Calibration materials are documented within each individual SOP.  
• All assays are calibrated in accordance with manufacturers’ guidance and as required as indicated by IQC performance.  
• Records of calibration are kept on the analysers. | • Refer to individual assay SOPs on QPulse  
• Refer to LP/PA/CB/OP32 – Clinical Biochemistry and Immunology Internal quality control procedures |
| IQC | • IQC is analysed as detailed within the associated SOP.  
• IQC failure as detailed in the associated SOP is investigated. |  |
## EQA
- All analytes registered on an associated EQA scheme (or sample exchange scheme if EQA scheme not available).
- Senior BMSs review EQA reports and feedback at monthly Quality Assurance Group meetings.
- Poor performance is identified and corrective/preventative measures are sought and reported.
- Minutes of meetings are disseminated to all staff.

## Interference
- Interferences for each assay are detailed within each SOP.
- Food stuffs and medication that need to be avoided for certain tests (e.g.: 5HIAA, urinary metadrenalines) are detailed within the patient information leaflets.
- Summary of the levels of interference from haemolysis, icterus and bilirubin is detailed within the associated SOP.

## Standard operating procedures
- All tests/procedures are undertaken following standard operating procedures. This helps to ensure that any procedure is carried out in a controlled order with no deviation from the detailed process.
- All SOP’s are reviewed regularly and all staff are able to highlight any changes required via Q-Pulse.

## Refer to SOP
- Individual assay SOP’s can be found on Q-Pulse.
- Refer to patient information leaflets.
- Refer to SOP LP/PA/CB/OP106 – Action on serum indices.
Post Examination

<table>
<thead>
<tr>
<th>Sources of uncertainty</th>
<th>CDDFT method of identification and minimisation</th>
<th>Associated documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report</td>
<td>All reports are issued in a standard format as described in associated SOP.</td>
<td>Refer to SOP LP/PA/GR004 – Results/Report SOP</td>
</tr>
<tr>
<td></td>
<td>Results are reported with associated reference ranges and comments.</td>
<td>Refer to SOP LP/PA/CB/OP93 – Amending reports.</td>
</tr>
<tr>
<td></td>
<td>Reports are amended following the protocol outlined in the associated SOP.</td>
<td></td>
</tr>
<tr>
<td>Reference ranges</td>
<td>Reference ranges are provided by manufacturers and the utility of these are discussed within the Clinical Biochemistry Group before implementation. For those where further investigation is required, a method comparison is undertaken.</td>
<td>Refer to SOP LP/PA/CB/OP96 – Evaluation of Instrumentation and methods.</td>
</tr>
<tr>
<td></td>
<td>Any change in reference range is highlighted to the users in WinPath following full evaluation. Dual reporting is undertaken where deemed appropriate by the Head of Department.</td>
<td>Refer to LP/PA/CB/OP220 – Reference range sources</td>
</tr>
<tr>
<td></td>
<td>The Clinical Scientists within the department also monitor national developments with regards to harmonisation of ranges and implement where appropriate.</td>
<td></td>
</tr>
<tr>
<td>Abnormal result alerts (within WinPath)</td>
<td>Abnormal alerts are set up within the LIMS systems.</td>
<td>Refer to LP/PA/BHI/IT004 - Biochemistry Authorisation Queues</td>
</tr>
<tr>
<td></td>
<td>Qualified BMS staff review the analytical validity of abnormal results.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Analytical ranges are highlighted within each assay SOP, WinPath and to users on reports.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delta checks are devised by the Clinical Scientists and implemented within WinPath.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal results may be highlighted to the Duty Biochemist/Consultant Immunologist to review them in a</td>
<td></td>
</tr>
</tbody>
</table>
### Clinical Context

- Telephoning abnormal results is undertaken following associated SOP.

### Interpretation

- Clinical interpretation is undertaken by appropriately trained staff who have or are undertaking the FRCPath examination.
- Automated comments have been created by Clinical Scientists in discussion with Clinicians to aid interpretation.

- Refer to SOP LP/PA/CB/OP105 – Telephone procedure.
Calculation of Uncertainty within CDDFT

Within the examination process the laboratory can calculate the measurement of uncertainty that is associated with each analyte. We can use our internal and external quality performance checks to assess the individual uncertainties within the measurement system. For further information on our internal and external quality control systems please refer to the relevant SOPs – LP/PA/CB/OP31 and LP/PA/CB/OP32.

The MU is the quantification of doubt, not error. The co-efficient of variation (CV%) or standard deviation (SD) can be considered as the combined uncertainty for results around the mean of a particular concentration of quality control material.

CDDFT process

An excel spreadsheet has been set up to facilitate the collection and calculation of the laboratory MU. Data (Running CV% and SD from IQC) will be collected and reviewed twice per year using from the analysers (September and March). Six months is deemed a suitable time period for review as this will reflect changes of lot of reagents, numerous calibrations and capture any random and systematic errors that arise. Where IQC lot changes arise within a 6 month period, the longest period of time where one lot has been used will be taken. Where IQC lot changes occur frequently, a review of lot to lot CV(%) and SD will take place for each analyte.

Minimum analytical goal

The minimum analytical goal enables the combination of analytical variation (CVa) and biological variation (CVi) to be reviewed and is a suitable candidate for target measurement uncertainty.

The minimum analytical goal is expressed as CVa <0.75 CVi

- Analytical variation is generated from the CV(%) of each level of internal quality control material for each analyte. This is done for each analyser and input into the spreadsheet.
- Biological variation (where available) has been taken from Westgard (www.westgard.com)
- Where biological variation is not available the analytical CV and SD of the assay will be reviewed to determine acceptability.

Standard Deviation

Standard deviation (SD) reflects the dispersion of results from the average and is used to measure confidence in the assay performance. SD can be considered as the combined standard uncertainty around a particular IQC concentration. SD of the IQC reflects the combined effect of all individual uncertainties arising in a measurement system.
The SD for each assay is set either by internal analysis of IQC data or from the manufacturer’s guidance depending on the material and the assay. Any consistent breeches in SD are discussed at the Clinical Biochemistry Quality Group.

The SD for each analyte is input into the MU spreadsheet. The SD is then multiplied by 1.96 to generate the Uncertainty of Measurement.
Calculated Tests

If reported results are derived from more than one actual measurement, for example calculated tests, the uncertainty is calculated by combining the uncertainty components of the contributing analytes. Formula used depends how the calculation is derived and is based on the article written by White and Farrance, Uncertainty of Measurement in quantitative medical testing. Clinical Biochemistry Review Vol 25 Suppl (ii) November 2004.

To calculate uncertainty you add the contributions form the difference components using the square root sum of the squares rule. The point to note is to use SD if the equation requires addition or subtraction. If multiplication or division is used within the calculation then you use CV. For each calculation the average standard deviation (SD) or coefficient of variation (CV) for that analyte will be used. If a clinician requires specific result information this will then be calculated upon request depending on the analyser it was generated from.

This table lists the calculations offered within CDDFT and the formulae used to calculate the UoM. \( u = \) uncertainty for the tests specified. Following the UoM calculation detailed below the answer is then multiplied by 1.96 as detailed above to generate the overall uncertainty for the specified calculation.

<table>
<thead>
<tr>
<th>Calculated Test</th>
<th>Calculation set up within WinPath</th>
<th>UoM calculation</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion Gap</td>
<td>( [(\text{NA})+(\text{K})-(\text{CL})-(\text{TCO}_2)] ) d0</td>
<td>( \sqrt{u_{\text{NA}}^2+u_{\text{K}}^2+c_{\text{Cl}}^2+u_{\text{TCO}_2}^2} )</td>
<td>SD</td>
</tr>
<tr>
<td>Globulin</td>
<td>( [(\text{TP})-(\text{ALB})] ) d0</td>
<td>( \sqrt{u_{\text{TP}}^2+u_{\text{Alb}}^2} )</td>
<td>SD</td>
</tr>
<tr>
<td>Adjusted Calcium</td>
<td>Adjusted ( [\text{Ca}] = \text{Total [Ca]} - (\text{slope.[albumin]}+ (\text{mean total [Ca]}-\text{intercept [Ca]}) )</td>
<td>( \sqrt{u_{\text{Ca}}^2+u_{\text{Alb}}^2} )</td>
<td>SD</td>
</tr>
</tbody>
</table>
| GFR                      | \( [0.993 ^\text{(Age)}]
\( [(\text{Creat})*0.011312] \) d6
\( [(\text{EPII})*[(\text{EPIII}) d6
\( [(\text{EPI})^2*(\text{EP12})] d6
\( [(\text{EPIF})*[(\text{EPIX})*[(\text{EPIG})] d0 \) | Creatinine only analyte used within this calculation and so UOM of creatinine would be provided. | NA |
<p>| Cholesterol:HDL ratio    | ( [(\text{CHO})/([\text{HDL}]) ) d1 | ( \sqrt{u_{\text{CHO}}^2+u_{\text{HDL}}^2} ) | CV  |
| LDL cholesterol          | ( [-1*(\text{TG})*2.2-(\text{HDL})+(\text{CHO})] ) d1 | ( \sqrt{u_{\text{TG}}^2+u_{\text{HDL}}^2+u_{\text{CHO}}^2} ) | CV  |
| Non HDL cholesterol      | ( [(\text{CHOL})-(\text{HDL})] ) | ( \sqrt{u_{\text{CHO}}^2+u_{\text{HDL}}^2} ) | SD  |
| Protein:Creatinine ratio | ( [(\text{UP})<em>100000/(\text{UCRE})] ) d0 | ( \sqrt{u_{\text{UP}}^2+u_{\text{UCre}}^2} ) | CV  |
| Creatinine Clearance     | ( [(\text{UCRE})</em>(\text{VOL})*1000000/(\text{CREA})*6/(\text{UCP})] ) d0 | ( \sqrt{u_{\text{UCre}}^2+u_{\text{Vol}}^2+u_{\text{Crea}}^2} ) | CV  |</p>
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Formula</th>
<th>UoM Calculation</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microalbumin:Creatinine ratio</td>
<td>( [(UMA)/(UCRE)] ) ( d1 ) ( \sqrt{uUMA^2+uCRE^2} )</td>
<td>CV</td>
<td></td>
</tr>
<tr>
<td>Macroprolactin dilution</td>
<td>( [(PRPE)/(PRDI)] \times 100 ) ( d0 )</td>
<td>Prolactin is only analyte within this calculation and so the UoM of prolactin would be provided.</td>
<td></td>
</tr>
<tr>
<td>Free androgen index</td>
<td>( [(TEST)/(SHBG)] \times 100 ) ( d1 )</td>
<td>( \sqrt{uTEST^2+uSHBG^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>24 hour urine Sodium</td>
<td>( [(UNA) \times (VOL)/(UCP) \times 24] ) ( d0 )</td>
<td>( \sqrt{uUNA^2+uVol^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>24 hour urine Potassium</td>
<td>( [(UK) \times (VOL)/(UCP) \times 24] ) ( d0 )</td>
<td>( \sqrt{uUK^2+uVol^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>24 hour urine chloride</td>
<td>( [(UCL) \times (VOL)/(UCP) \times 24] ) ( d0 )</td>
<td>( \sqrt{uUCL^2+uVol^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>24 hour urine urea</td>
<td>( [(UU) \times (VOL)/(UCP) \times 24] ) ( d0 )</td>
<td>( \sqrt{uUU^2+uVol^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>24 hour urine creatinine</td>
<td>( [(UCRE) \times (VOL)/(UCP) \times 24] ) ( d1 )</td>
<td>( \sqrt{uUCRe^2+uVol^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>24 hour urine calcium</td>
<td>( [(UCA) \times (VOL)/(UCP) \times 24] ) ( d2 )</td>
<td>( \sqrt{uUCA^2+uVol^2} )</td>
<td>CV</td>
</tr>
<tr>
<td>Test</td>
<td>Formula</td>
<td>Uncertainty Calculation</td>
<td>CV</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------</td>
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</tr>
</tbody>
</table>
| **24 hour urine phosphate**   | \[\frac{(UPH0) \times (VOL)}{UCP \times 24}\] \[\sqrt{u_{UPH0}^2 + u_{Vol}^2}\] | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| **24 hour urine urate**       | \[\frac{(UUA) \times (VOL)}{UCP \times 24}\] \[\sqrt{u_{UUA}^2 + u_{Vol}^2}\]  | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| **24 hour urine magnesium**   | \[\frac{(UMG) \times (VOL)}{UCP \times 24}\] \[\sqrt{u_{UMG}^2 + u_{Vol}^2}\]  | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| **24 hour urine protein**     | \[\frac{(UP) \times (VOL)}{UCP \times 24}\] \[\sqrt{u_{UP}^2 + u_{Vol}^2}\]  | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| Transferrin saturation        | \[\frac{(IRON) \times 100}{TRF}/28.6\] \[\sqrt{u_{Iron}^2 + u_{TRF}^2}\]  | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| Urine urate:creatinine ratio  | \[\frac{(UUA)}{(UCRE)}\] \[\sqrt{u_{UUA}^2 + u_{UCre}^2}\]  | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| Free Kappa:Free lambda ratio  | \[\frac{(KFLC)}{(LFLC)}\] \[\sqrt{u_{KFLC}^2 + u_{LFLC}^2}\]  | UCP – collection period assume no error  
  uVol – uncertainty of volume assumed to be 10% | CV                 |
| **AKI**                       | National algorithm embedded into LIMS.                                  | Creatinine is only analyte within this calculation and so the UOM of creatinine would be provided. |
Bias observed from EQA performance or identified through daily IQC checks will be brought to the attention of the Clinical Biochemistry and Immunology Quality Group where appropriate action will be taken. This will include completing an EQA performance investigation checklist LP/PA/GP/FORM3 and ensuring that to resolve any developing bias are performed. Any significant bias will be reported to the manufacturer.

Reporting problems

The following are scenarios where action will be taken with regards to the data used to assess MU:

- Data breaching minimum analytical goal
- Data with wide CV% (Chair of Quality Group and Head of Department review of what is an acceptable CV)
- Data where the 2SD limit is breeched
- Consistently poor performing EQA
- A MU value that does not improve from the previous calculation where previously unacceptable, or significant increase in MU.

Under the above circumstances, the data will be discussed at the Clinical Biochemistry Quality Group. An internal investigation will be instigated to determine any in-house contributors to a poor performance. This will involve review of IQC performance, EQA performance, Calibration checks, lot documentation and review of any possible lot variation. If an internal cause cannot be identified the data will then be forwarded to the manufacturer to assess if other users are experiencing similar issues and what resolution can be found.

As the MU data is collated on a 6 monthly basis it should be noted that analytical problems should be raised at the monthly Quality meetings following monthly reviews of IQC and EQA. Data with wide CVs, data where the IQC 2 SD limit is breeched and poor performing EQA should be highlighted during monthly review of the assays. These are reported to the manufacturer during the Quality Meeting or via the Siemens helpdesk (or to other relevant manufacturer as appropriate).

Data breaching the minimum analytical goal at the 6 month review will be discussed with Siemens at the Quality Group Meeting. It should be noted that when reviewing breaches you must take into account the level of IQC that is used to generate the data and the clinical significance of this level. Siemens are then expected to collate the MU data for all users and if required assess what improvements may be required.

For MU data that does not improve from the previous calculation, an assessment will be made by the Clinical Scientist as to the significance of the change. If concerns exist and these have not been communicated to
Siemens previously then Siemens will be consulted via the helpdesk or Field Application Specialist (for non-Siemens assays, the relevant manufacturer will be informed).

**Training**

All staff are required to be suitably trained in procedures before undertaking them independently without supervision. Competency to undertake procedures would be documented within their training and development files. Competency is re-assessed on a bi-annual basis unless an identifiable training need is brought to the attention of the Senior BMS. Please refer to the Pathology Education and Development Policy MPPAGPTR001 for further information.

The roles which each member of staff are expected to undertake are documented within their associated job description. These can be found on Q-Pulse and in the individual's personal file.

**Audits**

Monthly audits are arranged by the Clinical Biochemistry Quality Assurance Group.

External assessments are undertaken by UKAS. A full inspection is carried out every four years, with a surveillance visit every year.

**Incident reporting**

The Trust reporting system Safeguard is used to document and incidents. Please refer to the Trust intranet for further information on the safeguard process.