Critical appraisal checklist for papers on biological variation

Dr Bill Bartlett
Biological Variation Working Group
EFLM
Biological Variation Data

- Validity
  - Setting Quality Specifications
  - Assessing Significance of Change
- Application
- Generation
  - Methods for Collection of numerical data
  - Subjects
  - Samples
    - Sample Analysis. “Optimal Conditions Precision”
  - Data Analysis
  - Data sets produced
- Utility of population based reference values
- Other applications
These fundamental data have many applications that under-pin our practice!

These are reference data!

Do I have confidence in the data and understand their limitations?

Rodin’s Thinker
Burrell Collection Glasgow
“The components of the human organism are subject to variation caused by physiological processes, genetic differences, diseases and environmental factors. A rational interpretation of laboratory results demands knowledge of the variation of these components in the individual under study or in one or more adequately defined sets or reference individuals. An important task for clinical chemists and haematologists is therefore to provide relevant sets of reliable reference values.”

IFCC Expert panel on the Theory of Reference Values

1. The Concept of Reference Values. 1987;25:337-342
2. The selection of Individuals for the Production of reference values. 1987;25:639-644
3. Preparation of individuals and collection of specimens for the production of reference intervals. 1988;26:593-598
4. Control of analytical variability in the production of reference values. 1991;29:531-535
6. Presentation of observed values related to reference values. 1987;25:657-662

J Clin Chem Clin Biochem
Given their importance, we should have accepted standards for production and characterisation of BV Data!
Standard for Production

- Experimental Design
- Data Analysis

Standard for Reporting

- Enable Critical Appraisal
- Enable Transportability
- Minimum data set

Standard for Transmission

- Data Archetype?
- Transportability & Valid Application
“Our hope is that the comparability of such data might be provided by use of a common study design and analysis of data”

Fraser & Harris 1989
A few factors to consider:

- Validity
  - Setting Quality Specifications
  - Assessing Significance of Change
  - Utility of population based reference values
  - Other applications

- Biological Variation Data
  - Methods for Collection of numerical data
    - Selection of Subjects
      - Number of subjects
      - Number
    - Samples
      - Minimise pre-analytical variation
      - Stable samples
      - Un-stable samples
      - Minimise bias and maximise precision
    - Sample Analysis: “Optimal Conditions Precision”
      - Outlier Identification:
        - model only applies if the data is homogenous and representative of the underlying distribution and devoid of outliers. This process is therefore essential.
      - Estimating Component of Biological Variation: Performed after outlier removal
        - $S_{\text{total}} = S_{\text{w}} + S_{\text{i}} + S_{\text{e}}$
        - Where $S$ is the variance, variances enable combined data to be appropriately manipulated via a nested analysis of variance. The equivalent Standard Deviations are equivalent to the square root of $S$ giving $S_{\text{within}}$, $S_{\text{i}}$, $S_{\text{e}}$, and $S_{\text{total}}$ respectively.
    - Data Analysis
      - Data sets produced
        - $SD$ and $CV$: analytical imprecision of the assay used.
        - $SD_{\text{w}}$ and $CV_{\text{w}}$: average within-subject biological variation
        - $SD_{\text{e}}$ and $CV_{\text{e}}$: average within-subject biological variation
And a few more!
What is the uncertainty surrounding these data?
What are the quality standards for BV Data?
Confidence Intervals and Power Calculations for Within-Person Biological Variation: Effect of Analytical Imprecision, Number of Replicates, Number of Samples, and Number of Individuals

Thomas Røraas, Per H. Petersen, and Sverre Sandberg
Clinical Chemistry 58:91306–1313 (2012)

- design of an experiment to estimate biological variation should take into account the analytical imprecision.
- Estimates of biological variation should always be reported with confidence intervals (CIs)
Factors affecting confidence intervals around $CV_I$ and $RCV$

- **Study design:** number of subjects, number of samples, number of replicates.

- The effects of variables vary with the **ratio of $CV_A$ to $CV_I$**
  - Low ratio = narrower CI around estimate $CV_I$
  - Low ratio = higher power study

- **Number of samples more important than number of subjects**
Systematic Review of Data on Biological variation of ALT, AST and GGT.

Urinary Albumin Excretion.

CV_I  4% to 103% with central tertile 28% to 48%

40 studies with confounding factors:
- Time period over which samples were collected
- Study design
- Type of sample and concentration range studied
- Population studied and state of health
- Preanalytical factors
- Poorly described statistical methods

- Highlights the need for this approach

  “Nine recruited studies were limited by choice of analytic methodology, population selection, protocol application and statistical analysis”

Issues:

- Heterogeneity in experimental model
- Length of study inappropriate (3 days to 6 months)
- Methods with differing specificities
- Statistical methods not specified
Summary

- BV data are complex reference data
- Need for standards
- Safe application requires prior critical appraisal
- Published data are of varying quality
- Need to identify a minimum set of attributes to enable the data to be effectively transmitted and applied (archetype).
- Confidence intervals critically dependant upon ratio of $CV_A$ to $CV_I$. 

Standard for Reporting
Standard for Reporting

50 years of data

- Do the data travel through time
- Method developments

Quality

- Enough reported detail.
- Good Design?
- Inconsistency Terminology

Transportable

- Population demographics.
- Healthy?
- Diseased?

Translated into databases

- Excellent Resources
- Granular enough?
- Data archetype required?
Desirable Specifications for Total Error, Imprecision, and Bias, derived from intra- and inter-individual biologic variation

This most recent and extensive listing of biologic goals has been provided by Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. “Current databases on biologic variation: pros, cons and progress.” Scand J Clin Lab Invest 1999;59:491-500. This database was most recently updated in 2012.

Annex I, Part I: Within-subject and between-subject CV values of analytes and Desirable Analytical Quality Specifications for Imprecision, bias and total error

### Biological variation database: structure and criteria used for generation and update

Perich et al CCLM 2014

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Biologic Variation</th>
<th>Minimum Specification</th>
</tr>
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<tr>
<td></td>
<td>CV&lt;sub&gt;i&lt;/sub&gt;</td>
<td>CV&lt;sub&gt;B&lt;/sub&gt;</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td>5.9</td>
<td>16.3</td>
</tr>
<tr>
<td>α2-Antiplasmin</td>
<td>6.2</td>
<td>---</td>
</tr>
<tr>
<td>α2-Macroglobulin</td>
<td>3.4</td>
<td>18.7</td>
</tr>
<tr>
<td>α-Amylase</td>
<td>8.7</td>
<td>28.3</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>13.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Acid phosphatase tartrate-resistant</td>
<td>8.0</td>
<td>13.3</td>
</tr>
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Utility of Reference Values

1. These are only meaningful and transferable/transportable if defined for the population or individual in terms of:
   - Inclusion and exclusion criteria
   - Intake of food & drugs
   - Physiological and environmental conditions
   - State of well being
   - Specimen collection criteria
   - Performance characteristics of the analytical method
   - The statistical methods used for estimation of the limits
Critical Appraisal Checklist
The objective of the STARD initiative is to improve the accuracy and completeness of reporting of studies of diagnostic accuracy, to allow readers to assess the potential for bias in the study (internal validity) and to evaluate its generalisability (external validity).
Standards for Transmission
Utility of Reference Values

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- Intake of food & drugs
- Physiological and environmental conditions
- State of well being
- Specimen collection criteria
- Performance characteristics of the analytical method
- The statistical methods used for estimation of the limits
Minimum Data Set: BiVarC MDS

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<td>Data rating- new concept to be developed to indicate the quality of the BV data against a set of key criteria.</td>
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Granularity
- Drill down into detail (needs to be reported)
- Detail needs to be available and understood
- Use of standardised terminology and coding.
  - Terminology Simundic et al Clinical Chemistry November 2014
  - C-NPU, LOINC, SNOMED-CT

Definition of a Data Archetype required.
Are coding systems granular enough? :
Serum creatinine in Diabetes Stage 3 CKD:

- **C-NPU**: NPU04998 P Creatininium; subst.c.(enz.) = ? µmol/L
- **LOINC**: 14682-9  Serum / Plasma Creat SerPl-sCnc umol/L
- **SNOMED CT**: **Concept ID**: 731000119105
  Chronic kidney disease stage 3 associated with type 2 diabetes mellitus (disorder)
Databases & BiVarC Minimum Data Set

Use of recognised coding systems as metadata?
BiVarc MDS - Domain 1

- Analyte Name
  - C-NPU LOINC
  - Method reference
  - Other
    - Method modifications

- Measurement Procedure
  - EDTA
  - Citrate
  - Lithium Heparin
  - Sodium Heparin

- Plasma
  - Plain tubes
  - Gel separating tubes

- Serum
  - preservatives/stabilisers

- Urine
  - Preservative/stabiliser
  - anti-coagulant used

- Fluid
  - Whole Blood

- Units of measurement
  - Other

- Target

- Matrix
  - Serum
  - Urine
  - Fluid

- BiVarc Minimum Data Set

- Population Characteristics
BiVarC MDS - Domain 2

BiVarC Minimum Data Set

Population Characteristics

Demographics
- Number of Subjects
- Gender Split
- Age Range
- Ethnicity
- Geographical Location
- Ostensibly Healthy
- Qualifying statement

State of Well Being
- Diseased
- SICMED Code
- Staging of Disease

Medication
- Contraceptive Pill
- Prescribed by medical professional
- Vitamins
- Trace elements
- Other

Physical/Physiological characteristics
- BMI
- Blood Pressure
- Stage of menstrual Cycle
- Menopausal

Other
- Diet
- Alcohol
- Dietary
- Exercise
- Smoking History
BiVarC MDS - Domain 3

BiVarC Minimum Data Set

1. Target
2. Population Characteristics
   - Duration of Study
   - Number of Samples per Subject
   - Patient State at time of Sampling
     - Fasting
       - Length of fast
     - Qualifying Statement
     - Supine/erect/sitting
       - Length of time
   - Frequency of Sampling
   - Timing of Samples
     - Time of day
     - Season of year
   - Sampling procedure
   - Number of replicate Analyses
   - Power of study
     - To identify Biological Variation Indices With Confidence
     - To identify Heteroscedasticity
   - Other qualifying statements
   - Compliant with Biological variation Checklist
     - Yes
     - Qualification for inclusion in Database
     - No

4. Data Characteristics

5. Publication

6. Study BioVar Rating
BiVarC MDS - Domain 4, 5 & 6

To be developed
Standards for Production
Addresses uncertainty  Appropriately powered studies

Standards for Reporting
Delivers required granular detail  Ensures minimum data set present

Standards for Transmission
Enables safe contextual use of data  Enables accessibility to data

The Process

Checklist

MDS: Data Archetype

Safe accurate and effective application of BV data across health care economies
Table 1. Biologic Variation Data Reporting Checklist (BVdCR).

<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Item #</th>
<th>Item</th>
<th>Evidence</th>
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<tbody>
<tr>
<td><strong>Title/Abstract</strong></td>
<td>1</td>
<td>The title should indicate that the content relates to a study of biologic variation, the subject of the study, the sample matrix, and the population studied. Analytic, state of well-being, biologic variation, relevant clinical or patient data might be employed. e.g., [16], [22], [32], [33].</td>
<td></td>
</tr>
<tr>
<td><strong>Abstract</strong></td>
<td>3.1</td>
<td>An abstract should include the headline biologic variation data, the major characteristics of the population studied, and clearly identify the analytic, the method of measurements, the sample matrix and quantities studied, the statistical approach, the duration of the study and the geographical location of the study.</td>
<td></td>
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<tr>
<td><strong>Introduction</strong></td>
<td>2</td>
<td>Introduction should clearly identify the context and aims of the study and cite any previous relevant studies of biologic variation of the target analyte/measurement. Recommended terminology to be adopted or description of variability [1].</td>
<td></td>
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<tr>
<td><strong>Methods</strong></td>
<td>3</td>
<td>Described in enough detail to facilitate transportability of the derived data across populations and health care economics. The scope, the groups being studied, the number of participants, analytical data and their applicability require delivery of appropriately described and evaluated to enable their use as such.</td>
<td></td>
</tr>
<tr>
<td><strong>Analytical/ Measurement</strong></td>
<td>3.1 (A)</td>
<td>The described study should clearly identify the target analyte and measurement. Where available internationally agreed terminology and cutoffs should be utilized.</td>
<td></td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>3 (B)</td>
<td>The description of the subjects and population studied should be detailed enough to enable transportability of the biologic variation data set. Minimum data set should be present [15, 22, 23].</td>
<td></td>
</tr>
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<td><strong>Measurement Procedure</strong></td>
<td>3.1 (A)</td>
<td>A clear description of the analytical methodology used should form part of the metadata. This may be made available via an appropriate reference or be presented within the publication. Deviation from standard operating procedures, use of adaptations of published methods, and deviation from manufacturers’ recommended methods in the case of commercially available systems should be documented. Standardization and traceability should be clearly identified.</td>
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<td><strong>Length of Study</strong></td>
<td>3.1 (C)</td>
<td>Length of the study periods should be clearly identified.</td>
<td></td>
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<td><strong>Sample</strong></td>
<td>3.1 (D)</td>
<td>Sampling protocols that minimize pre-analytical variation should be adequately described to enable transportability of the data and numbers of samples taken sufficient to deliver the required power to the study [25, 26]. Sampling conditions and sample type should be described in detail. Pre-analytical storage conditions of samples should be described.</td>
<td></td>
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<td><strong>Sample size</strong></td>
<td>3.1 (E)</td>
<td>Sample size should be appropriate. The sample size should be stated and justified.</td>
<td></td>
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<tr>
<td><strong>Data analysis</strong></td>
<td>3.1 (F)</td>
<td>Recorded details should include the beginning and end date of the study and length of sampling. Data analysis methods and results from analysis should be presented. Analytical protocols should be designed to minimize sources of analytical variability [Optimal Conditions Procedures].</td>
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<td><strong>Data Analysis</strong></td>
<td>4</td>
<td>Data analysis techniques should be described. The power of the study to identify indices of biological variation should be calculated and presented [15].</td>
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<td><strong>Outlier analysis</strong></td>
<td>4.1 (C)</td>
<td>This examination must be undertaken. Outliers should be evaluated from the final analysis of the data. Test for outliers should be applied to all levels of data. The number of outliers and reasons for their exclusion must be given.</td>
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<td><strong>Heterogeneity of variance</strong></td>
<td>4.2 (C)</td>
<td>This examination must be undertaken. Subjects with large within subject variance should be excluded from calculations used to determine an estimate of common true variance. The numbers of outliers and reasons for their exclusion must be given.</td>
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<td><strong>Statistical methods described and appropriate</strong></td>
<td>4.3 (C)</td>
<td>Statistical methods used should be appropriately identified. It for purpose referenced. Data that do not conform to a normal distribution should be appropriately transformed.</td>
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<td><strong>Results</strong></td>
<td>5</td>
<td>Unified terminology [14] should be used and appropriately defined metadata clearly presented to enable understanding and transportation of the data through time and across health care systems.</td>
<td></td>
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<td><strong>Terminology</strong></td>
<td>5 (D)</td>
<td>Terms and symbols should be used to describe biological variation should conform standards identified by Terminology of the study.</td>
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<td><strong>Results clearly presented and managed</strong></td>
<td>5.2 (D)</td>
<td>Biologic variation data, with derived indices, should be tabulated in a format that enables extraction of the key data uniformly associated with a minimum data set to enable transportability of the data. Power of the study and confidence limits around estimates of biologic variation should be presented. The results section should clearly identify the results of outlier analysis undertaken and confirm homogeneity of the data sets if data are identified the parameters used to enable this should be clearly characterized.</td>
<td></td>
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<tr>
<td><strong>Discussion</strong></td>
<td>6</td>
<td>The discussion of the data should clearly include a focus on factors that impact on the transportability of the data to other settings. Limitations and strengths of the study should be addressed.</td>
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Table 1. Biological Variation Data Reporting Checklist (BiVarC).

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<td>Abstract</td>
<td>1.1</td>
<td>As a minimum it should indicate the headline biological variation data, the major characteristics of the population studied and clearly identify, the analyte, the method of measurement, the sample matrix and quantities studied, the statistical approach, the duration of the study and the geographical location of the study.</td>
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### Methods

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#### Analyte/Measurand.

3.1 (A) The described study should clearly identify the target analyte and measurand/s. Where available internationally agreed terminology and codings should be utilised.

#### Subjects

3.2 (B) The description of the subjects and population studied should be detailed enough to enable transportability of the biological variation data set. Minimum data set should be present [21, 22, 23].

#### Measurement Procedure.

3.3 (A) A clear description of the analytical methodology used should form part of the metadata. This may be made available via an appropriate reference or be presented within the publication. Deviation from standard operating procedures, use of adaptations of published methods, and deviation from manufacturers recommended methods in the case of commercially available systems should be documented. Standardisation and traceability should be clearly identified.

#### Length of Study

3.4 (C) Length of the study periods should be clearly identified.

#### Samples

3.5 (C) Sampling protocols that minimise pre-analytical variation should be adequately described to enable transportability of the data and numbers of samples taken sufficient to deliver the required power to the study. [25, 26]

Sampling conditions and sample type should be described in detail. Pre-analytical storage conditions of samples should be described. Recorded details should include the beginning and end date of the study and timings of sampling.

#### Conditions for analysis of samples

3.6 (C) A description of conditions under which the samples were analysed. Analytical protocols should be designed to minimise sources of analytical variability (Optimal Conditions Precision). [24]
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**Data Analysis**

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<td>(F) 6</td>
<td>For database</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>5</th>
<th><strong>Unified terminology</strong>[13]** should be used and appropriately defined metadata clearly presented to enable understanding and transportation of the data through time and across health care economies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td>5.1 (D)</td>
<td>Terms and symbols should be used to describe biological variation should conform standards identified by Simundic et al.[13]</td>
</tr>
</tbody>
</table>
| Results clearly presented and managed | 5.2 (D) | Biological variation data, with derived indices, should be tabulated in a format that enables extraction of the key data unambiguously associated with a minimum data set to enable transportability of the data.  
Power of the study and confidence limits around estimates of biological variation should be presented.  
The results section should clearly identify the results of outlier analysis undertaken and confirm homogeneity of the data sets. If data are stratified the parameters used to enable this should be clearly characterised. |
| Discussion | 6 | The discussion of the data should clearly include a focus on factors that impact on the transportability of the data to other settings. Limitations and strengths of the study should be addressed. |
Archetype: definition?

A computable expression of a domain content model.
Structured content to enable communication of key information.
• Derived as far as possible from historical studies
• Mandated for future studies
Standards required for production, reporting and transmission of BV Data.

A critical appraisal checklist has been developed to:
- enable assessment of historical data
- drive up quality of future publication

MDS/Archetype will enable transmission and safe contextual use of BV data across health care systems.

Summary
Route Forward?

www.biologicalvariation.com
Next Steps?

- Promotion of the checklist
- Definition of MDS/Archetype for application to future database developments.
- Development of supporting information sources/publications to enable understanding and compliance with the approach
- Standards?