

DH05: Laboratory Data: Issues with Multiple Reference Ranges and Methods of Normalisation

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Agenda

- Motivation
- Data
- Normalisation model and common reference range
- Results
- Conclusion

Motivation

- Lab data is required in clinical trials for safety reasons
- Multi-center trials: different laboratories
- Varied laboratory results and different reference ranges
- Combining the data can be a great challenge
- Usage of normalisation methods



Data

	Subject Identifier for the Study	Sex	Parameter	Paramet Code	Analysis Visit	Analysis Relative Day	Analysis Value	Reference Range
1	112	F	Creatinine (umol/L)	CREAT	VISIT 1	-1	42.2	35.36-61.88
2	112	F	Creatinine (umol/L)	CREAT	VISIT 5	22	55.04	35.36-61.88
3	112	F	Creatinine (umol/L)	CREAT	VISIT 7	43	51.04	35.36-61.88
4	112	F	Hemoglobin (g/dL)	HGB	VISIT 1	-8	13.1	12-16
5	112	F	Hemoglobin (g/dL)	HGB	VISIT 5	22	14.1	12-16
6	112	F	Hemoglobin (g/dL)	HGB	VISIT 7	43	11.5	12-16
7	125	F	Aspartate Aminotransferase (U/L)	AST	VISIT 1	-3	33	8-40
8	125	F	Aspartate Aminotransferase (U/L)	AST	VISIT 5	20	24	8-40
9	125	F	Aspartate Aminotransferase (U/L)	AST	VISIT 7	41	20	8-40
10	125	F	Creatinine (umol/L)	CREAT	VISIT 1	-3	77	70-106
11	125	F	Creatinine (umol/L)	CREAT	VISIT 5	20	72	70-106
12	125	F	Creatinine (umol/L)	CREAT	VISIT 7	41	70	70-106

- Generated dummy data
- Laboratory data of three different parameters
- 239 subjects
- 198 females, 41 males
- Analysis value with normal range lower and upper limit

Data

Parameter	Reference Range	Frequency Count
Aspartate Aminotransferase (U/L)	0-32	51
Aspartate Aminotransferase (U/L)	5-35	20
Aspartate Aminotransferase (U/L)	5-37	11
Aspartate Aminotransferase (U/L)	8-40	65
Creatinine (umol/L)	35.36-61.88	33
Creatinine (umol/L)	44-115	33
Creatinine (umol/L)	61.88-106.08	10
Creatinine (umol/L)	70-106	21

Sex	Parameter	Reference Range	Frequency Count
F	Hemoglobin (g/dL)	10-15	19
F	Hemoglobin (g/dL)	11-16	40
F	Hemoglobin (g/dL)	11.3-15.2	1
F	Hemoglobin (g/dL)	12-16	71
M	Hemoglobin (g/dL)	10-15	5
M	Hemoglobin (g/dL)	11-16	9
M	Hemoglobin (g/dL)	12-16	4
M	Hemoglobin (g/dL)	14-18	10

Location - scale model (Chuang-Stein)

- Normalise values relative to a selected set of reference ranges:

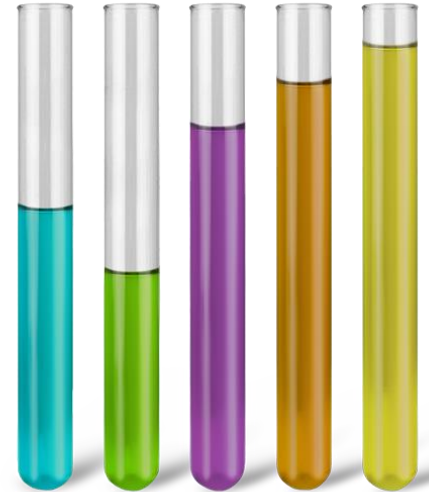
$$value_{std} = (value - LLN) * \frac{ULN_{std} - LLN_{std}}{ULN - LLN} + LLN_{std}$$

- Transformation preserves the distance from the lower limit of normal as a multiple of the specified range:

$$\frac{value - LLN}{ULN - LLN} = \frac{value_{std} - LLN_{std}}{ULN_{std} - LLN_{std}}$$

Choosing the common reference range

- Normalisation of results relative to a chosen standard reference range
 - Choose upper limit and lower limit as
 - Method 1: MAX(LLN) and MIN(ULN)
 - Method 2: Highest ULN (and highest LLN if more than one)
 - Method 3: Most frequent reference range



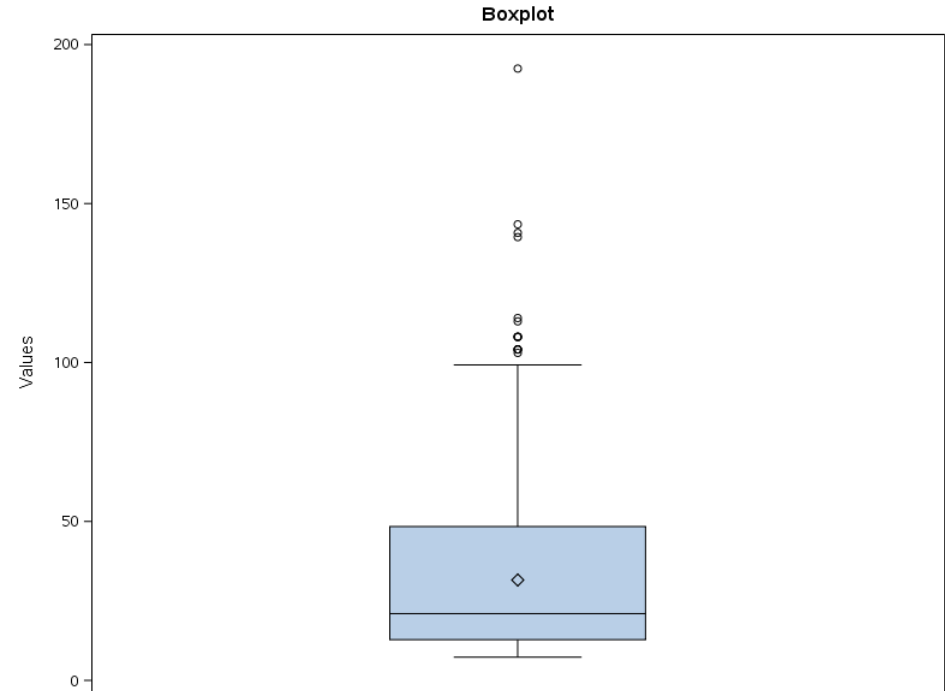
MAX(LLN) and MIN(ULN)

- Get maximum of LLN for every parameter
 - Get minimum of ULN for every parameter
 - Assign these as standard ranges
 - Merge to lab data
- Normalisation of values

```
DATA LAB1;  
  SET LAB;  
  IF anrlo ne . and anrhi ne . THEN  
    aval=(aval-anrlo)*(uln_std-lln_std)/(anrhi-anrlo)+lln_std;  
RUN;
```

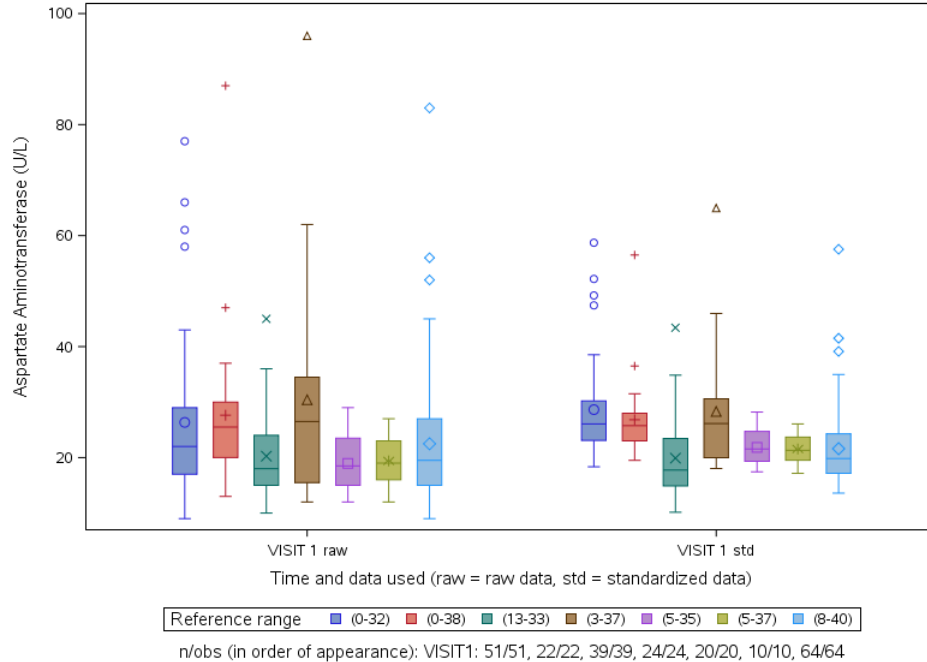
Box Plot

- Results are displayed as box plots
- SAS 9.4[®] procedure PROC SGPLOT with the VBOX statement
- Y-axis: result of a specific lab test

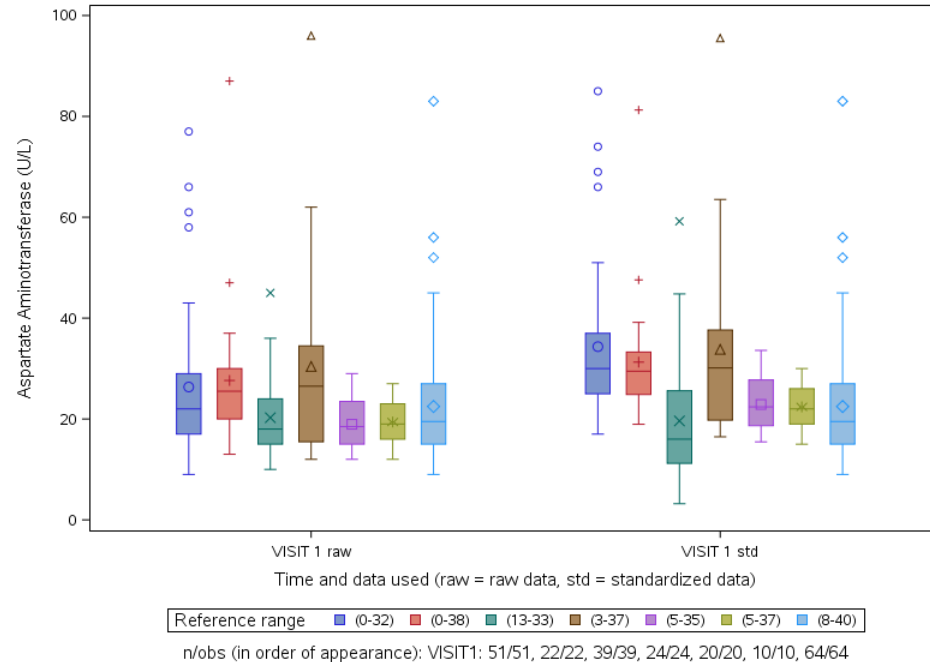


Aspartate Aminotransferase

Method 1: $\max(\text{LLN}) - \min(\text{ULN})$

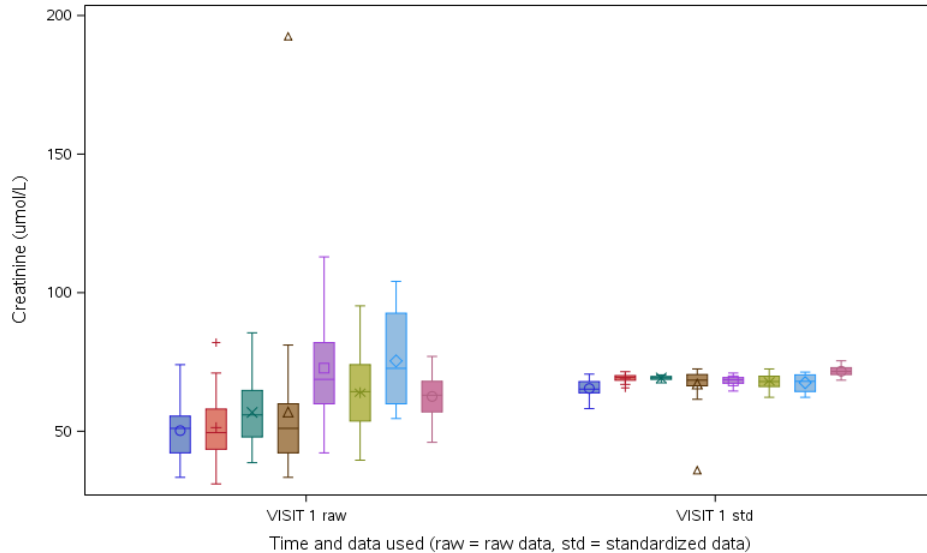


Method 2: highest ULN (and highest LLN)



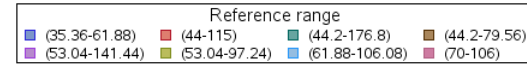
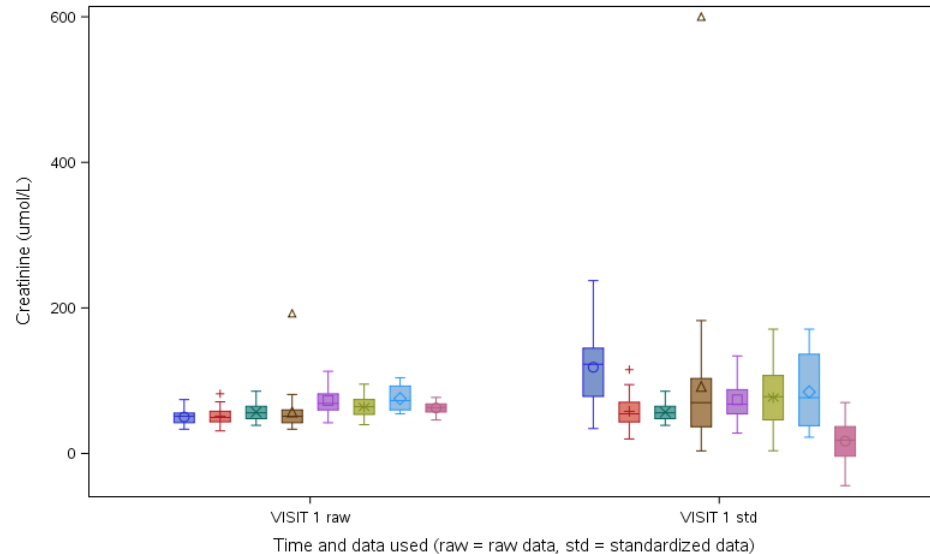
Creatinine

Method 1: $\max(\text{LLN}) - \min(\text{ULN})$



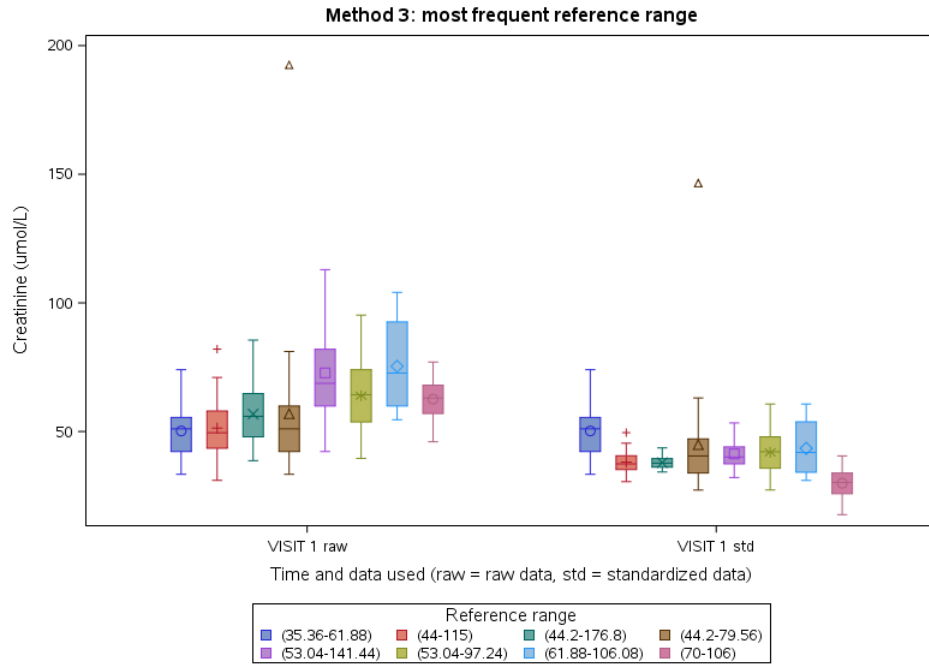
n/obs (in order of appearance): VISIT1: 31/31, 32/32, 12/12, 30/30, 24/24, 29/29, 10/10, 21/21

Method 2: highest ULN (and highest LLN)



n/obs (in order of appearance): VISIT1: 31/31, 32/32, 12/12, 30/30, 24/24, 29/29, 10/10, 21/21

Creatinine



n/obs (in order of appearance): VISIT1: 31/31, 32/32, 12/12, 30/30, 24/24, 29/29, 10/10, 21/21

Creatinine - Example

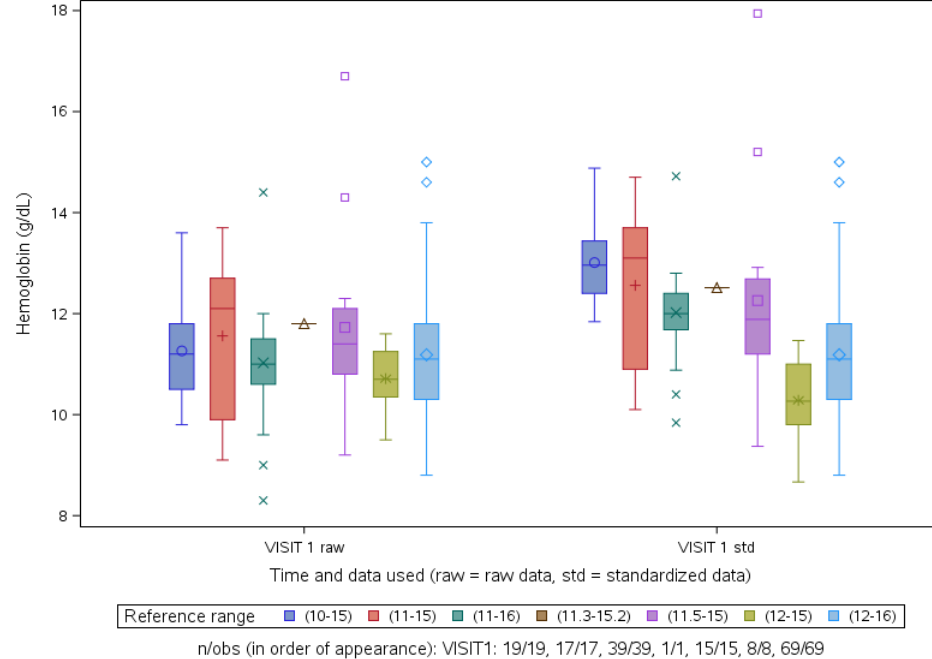
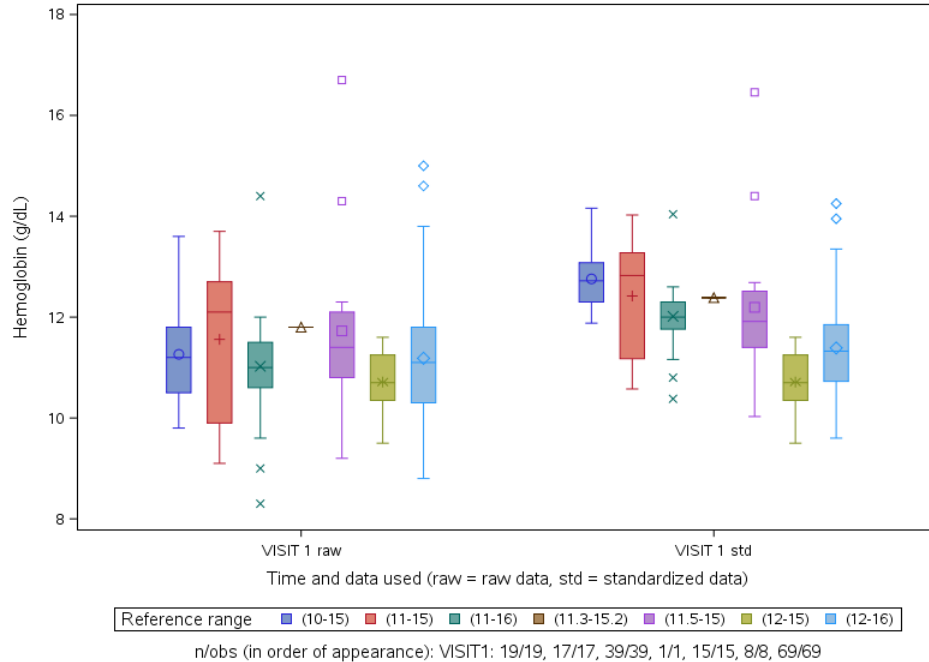
- In method 2 there is a statistical outlier
- Before normalisation the value is close to 200
- After normalisation the value is around 600

$$value_{std} = (\overset{\text{value}}{192.48} - \overset{\text{LLN}}{44.2}) * \frac{\overset{\text{ULN}_{std}}{176.8} - \overset{\text{LLN}_{std}}{44.2}}{\overset{\text{ULN}}{79.56} - \overset{\text{LLN}}{44.2}} + \overset{\text{LLN}_{std}}{44.2} = 600.25$$

Hemoglobin - Females

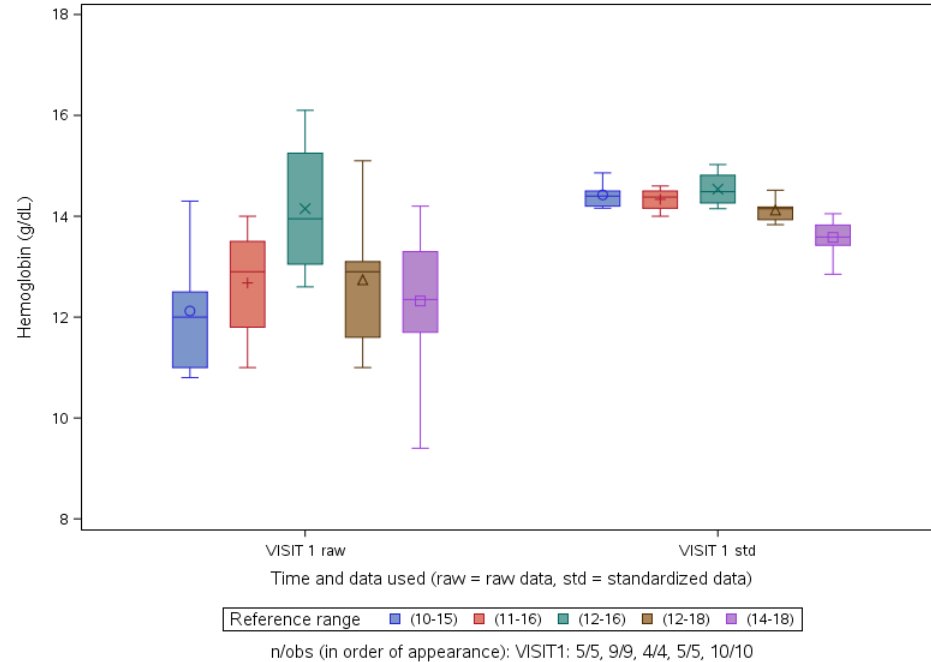
Method 1: $\max(\text{LLN}) - \min(\text{ULN})$

Method 2: highest ULN (and highest LLN)

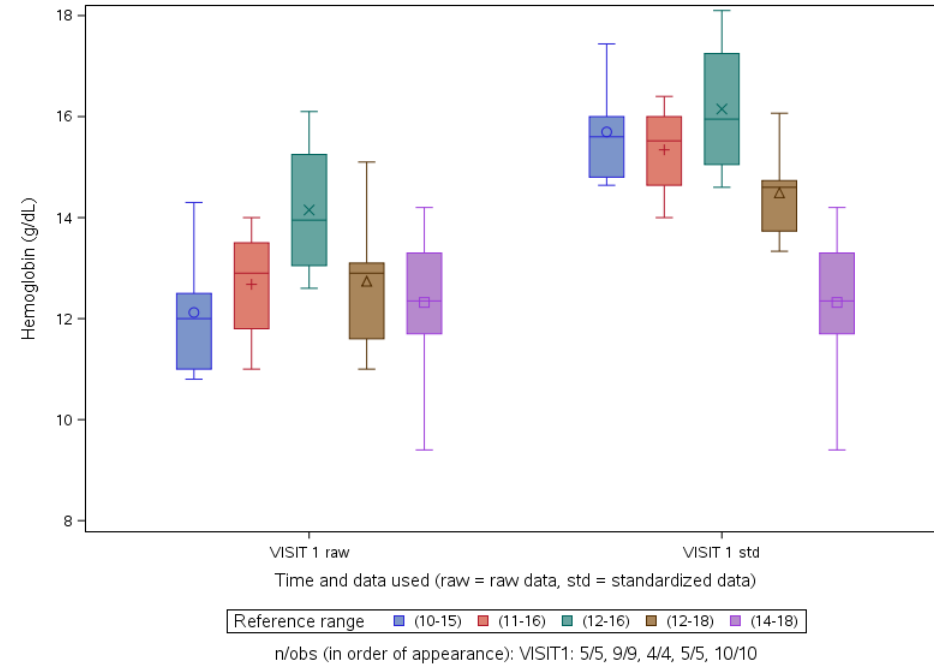


Hemoglobin - Males

Method 1: $\max(\text{LLN}) - \min(\text{ULN})$



Method 3: most frequent reference range



Summary

Location-
scale model

Reference
Ranges

Results of
Normalisation

Conclusion

- **Normalising laboratory data** can be a solution to combine data from different laboratories
- Better: Using a **central laboratory** whenever possible
- The selection of both the **normalisation model** and the **common reference range** is very important
- All laboratory parameters have different **clinical interpretations and statistical properties**

Normalisation should not be a blind procedure!

Thank you!

Any questions?

Contact Information

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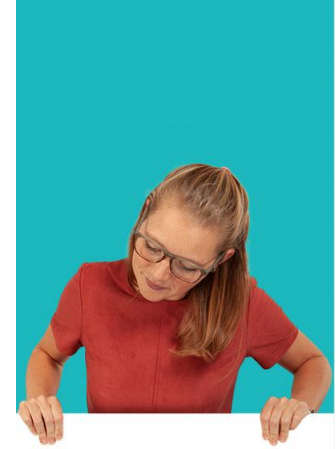
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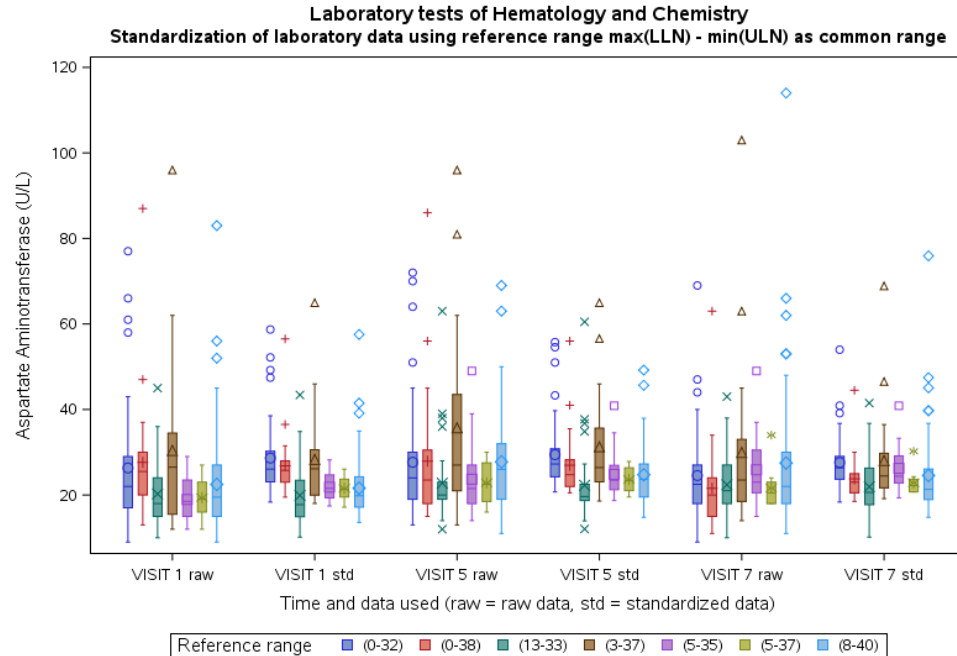
45131 Essen

Web: <http://www.chrestos.de>

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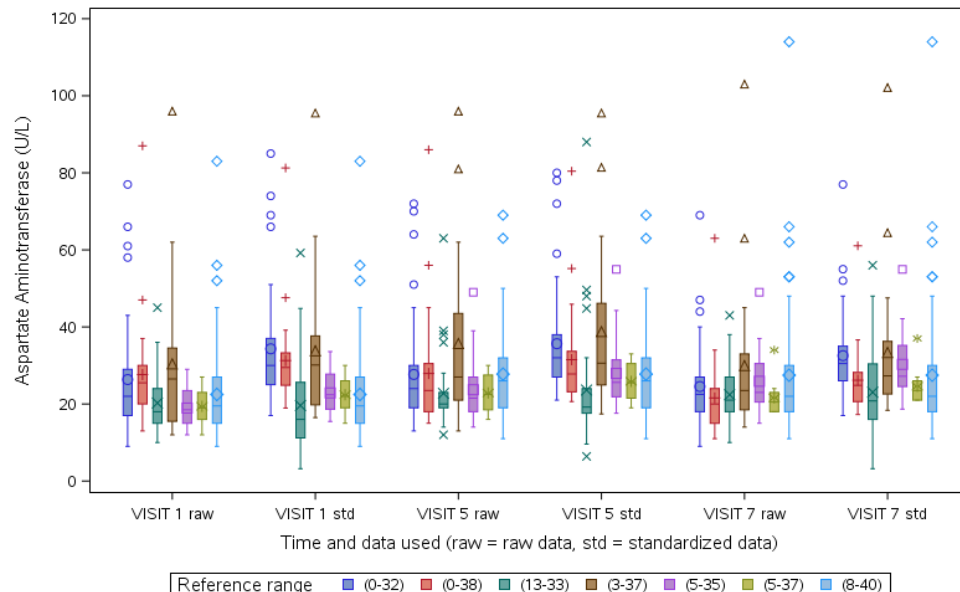
Aspartate Aminotransferase



n/obs (in order of appearance): VISIT1: 51/51, 22/22, 39/39, 24/24, 20/20, 10/10, 64/64, VISIT5: 49/49, 24/24, 41/41, 24/24, 20/20, 8/8, 63/63, VISIT7: 48/48, 21/21, 35/35, 20/20, 20/20, 10/10, 57/57

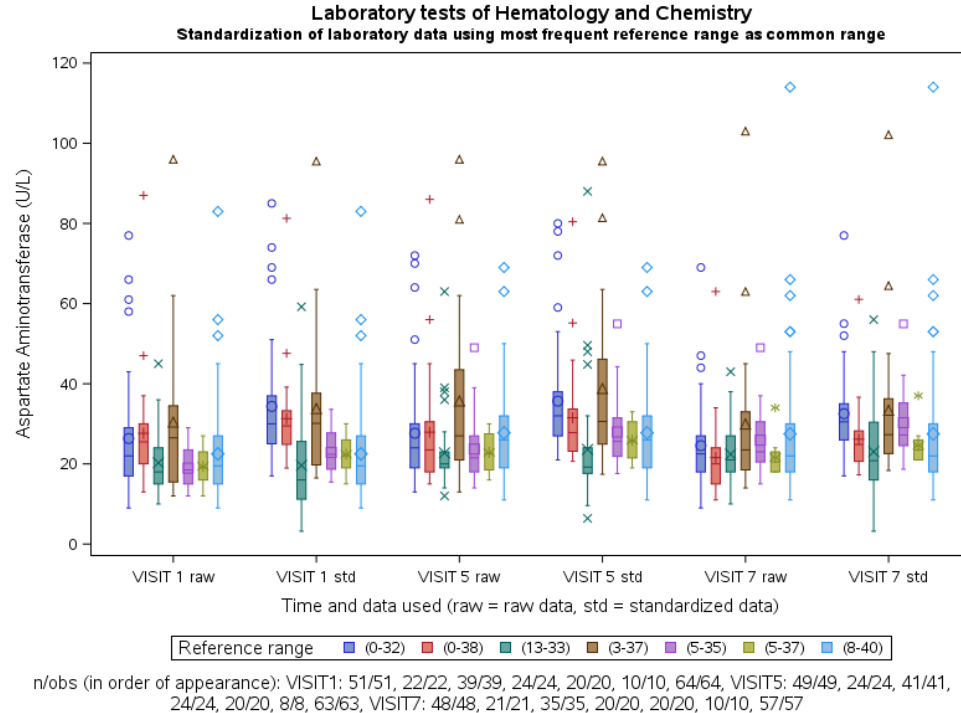
Aspartate Aminotransferase

Laboratory tests of Hematology and Chemistry
Standardization of laboratory data using reference range with highest ULN (and highest LLN if more than one) as common range

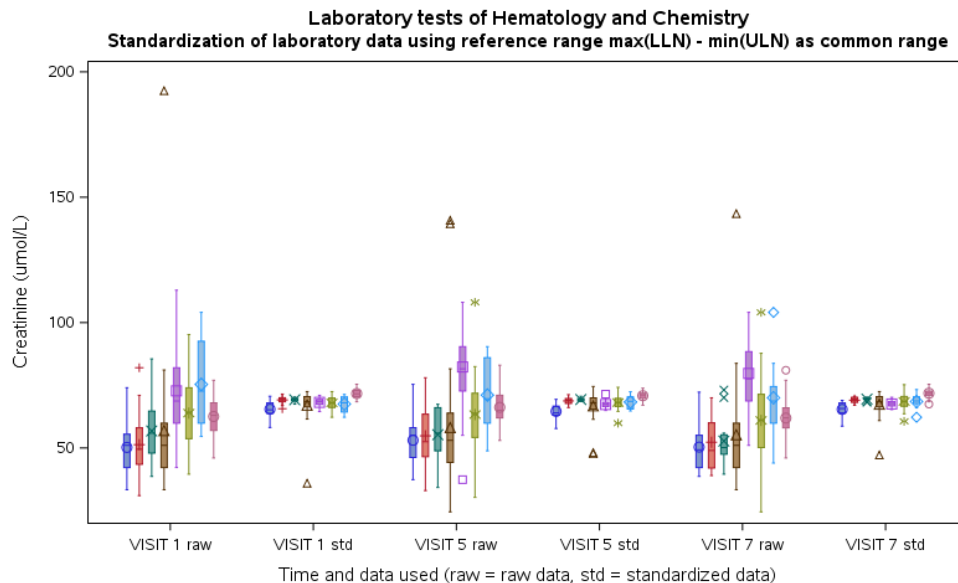


n/obs (in order of appearance): VISIT1: 51/51, 22/22, 39/39, 24/24, 20/20, 10/10, 64/64, VISIT5: 49/49, 24/24, 41/41, 24/24, 20/20, 8/8, 63/63, VISIT7: 48/48, 21/21, 35/35, 20/20, 20/20, 10/10, 57/57

Aspartate Aminotransferase



Creatinine

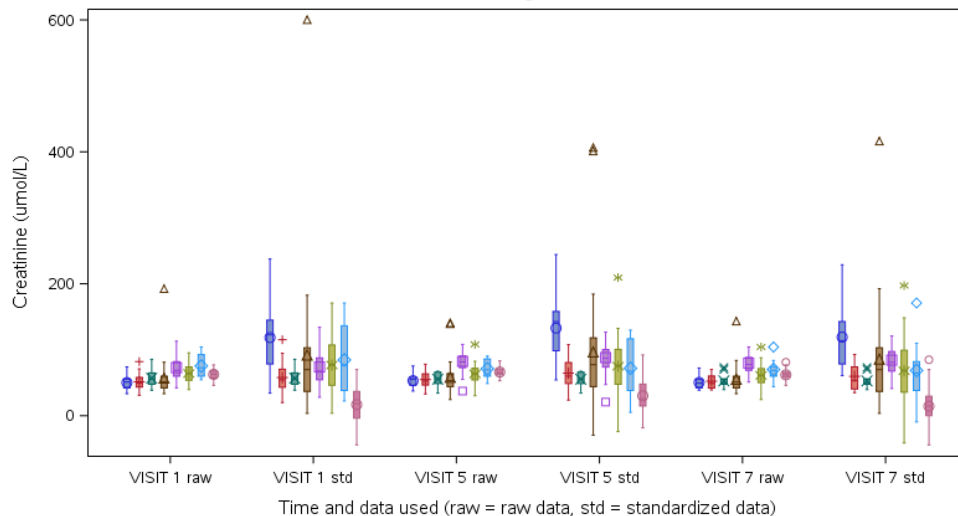


Reference range			
■ (35.36-61.88)	■ (44-115)	■ (44.2-176.8)	■ (44.2-79.56)
■ (53.04-141.44)	■ (53.04-97.24)	■ (61.88-106.08)	■ (70-106)

n/obs (in order of appearance): VISIT1: 31/31, 32/32, 12/12, 30/30, 24/24, 29/29, 10/10, 21/21, VISIT5: 33/33, 32/32, 14/14, 28/28, 24/24, 29/29, 10/10, 21/21, VISIT7: 27/27, 25/25, 12/12, 30/30, 20/20, 26/26, 9/9, 21/21

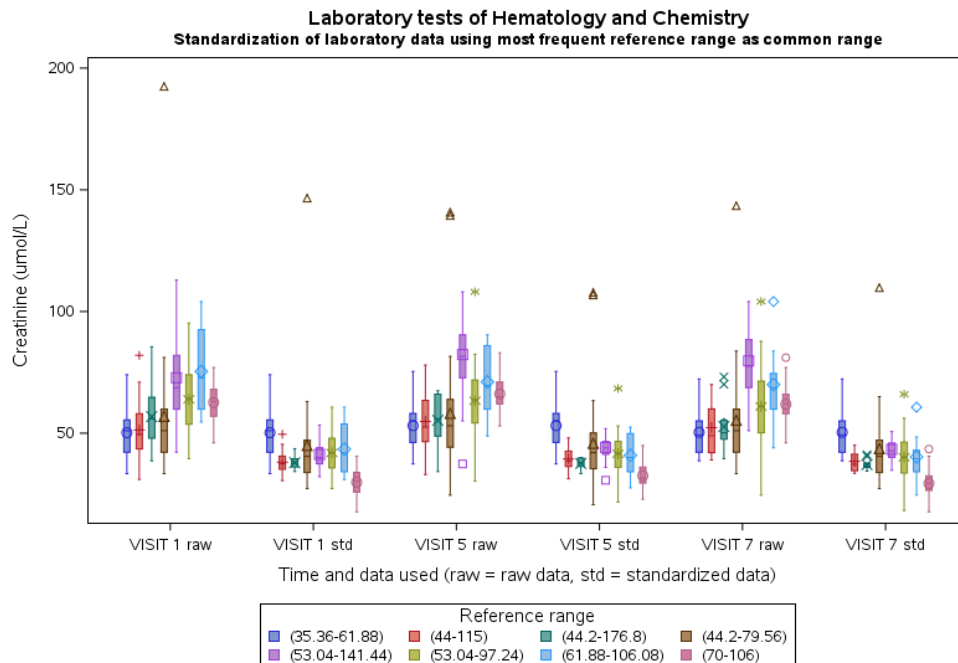
Creatinine

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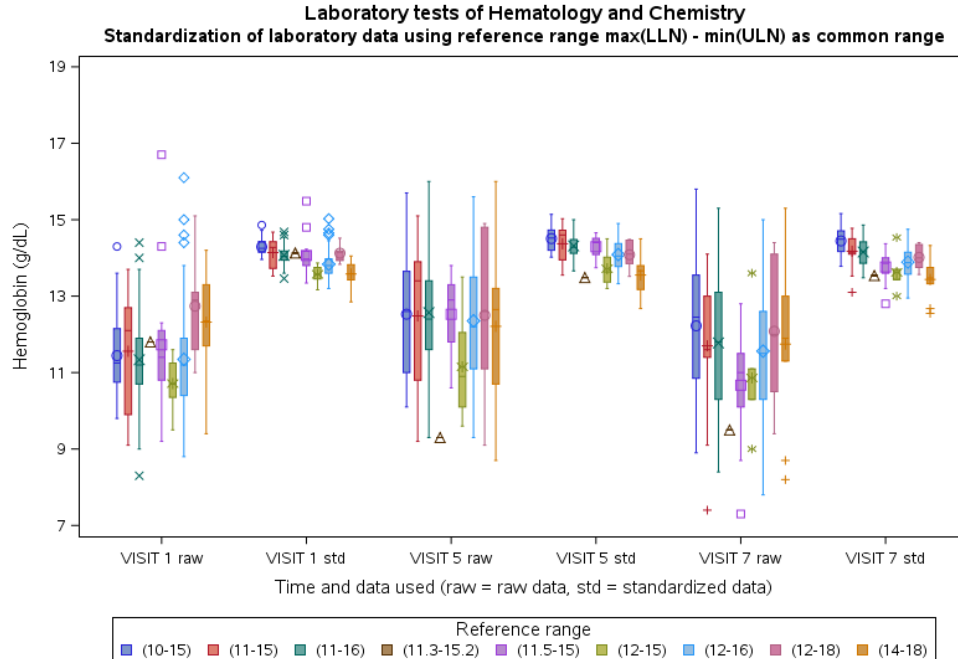
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Creatinine



n/obs (in order of appearance): VISIT1: 31/31, 32/32, 12/12, 30/30, 24/24, 29/29, 10/10, 21/21, VISIT5: 33/33, 32/32, 14/14, 28/28, 24/24, 29/29, 10/10, 21/21, VISIT7: 27/27, 25/25, 12/12, 30/30, 20/20, 26/26, 9/9, 21/21

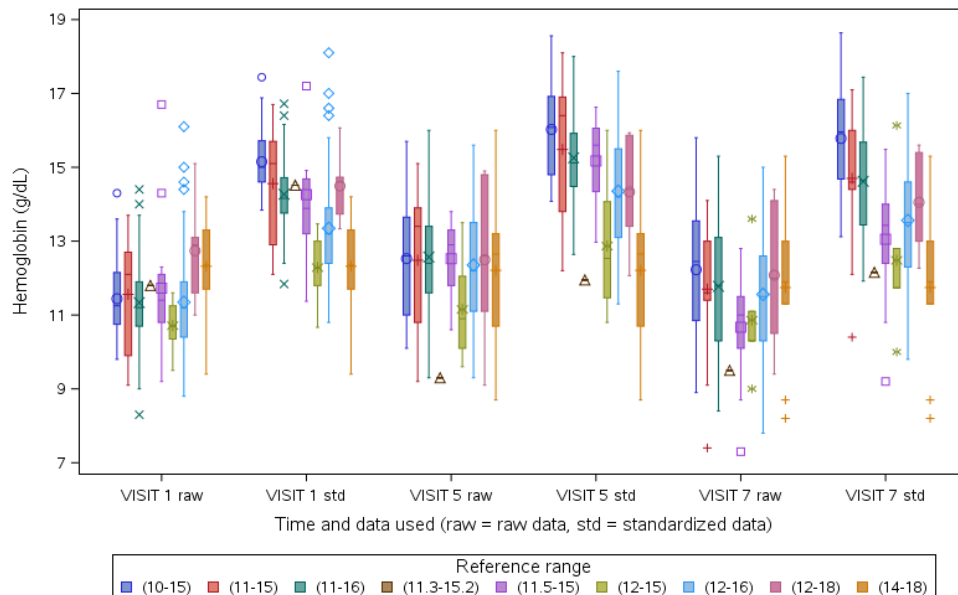
Hemoglobin



n/obs (in order of appearance): VISIT1: 24/24, 17/17, 48/48, 1/1, 15/15, 8/8, 73/73, 5/5, 10/10, VISIT5: 24/24, 17/17, 49/49, 1/1, 16/16, 8/8, 74/74, 5/5, 10/10, VISIT7: 20/20, 17/17, 45/45, 1/1, 13/13, 5/5, 70/70, 5/5, 9/9

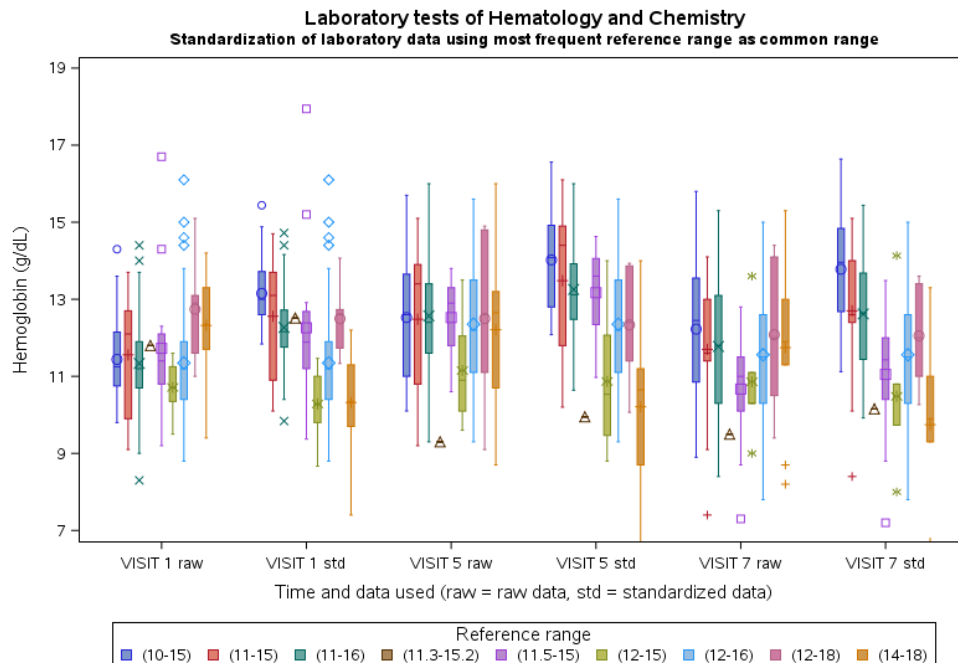
Hemoglobin

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Standardization of laboratory data using reference range with highest ULN (and highest LLN if more than one) as common range



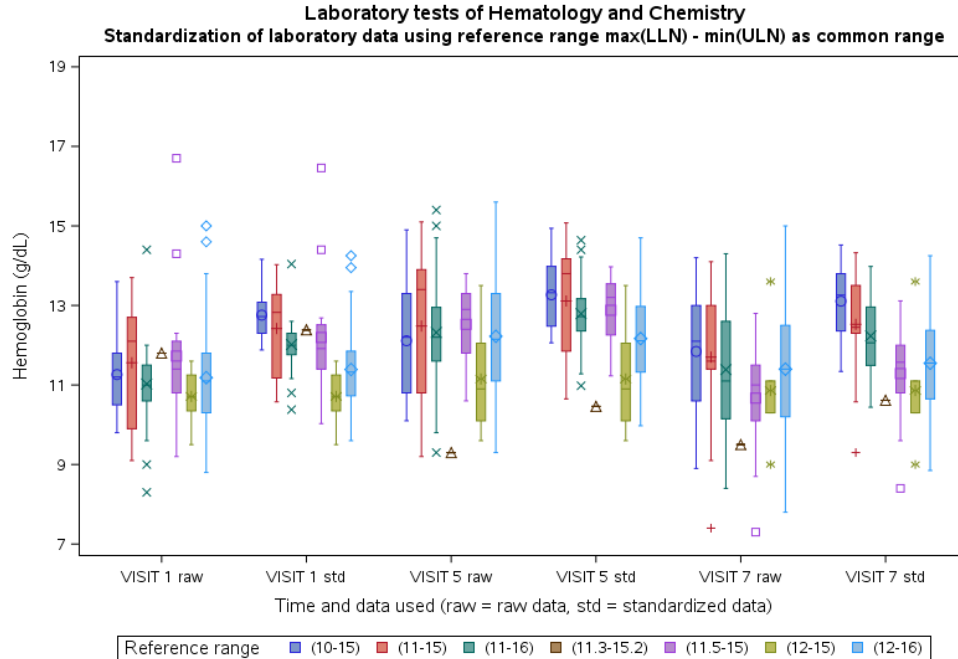
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Hemoglobin



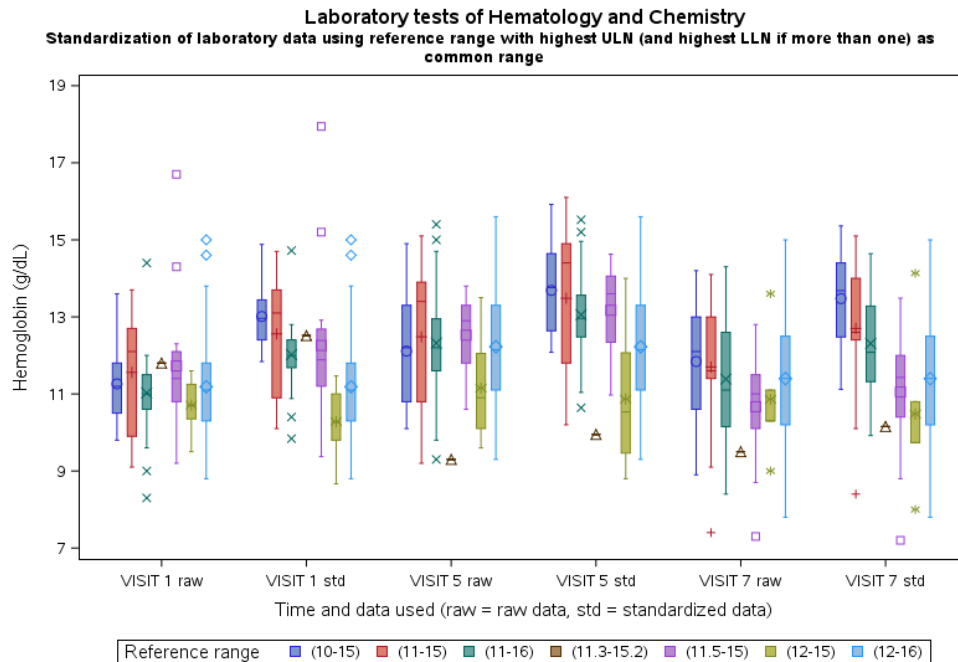
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Hemoglobin - Females



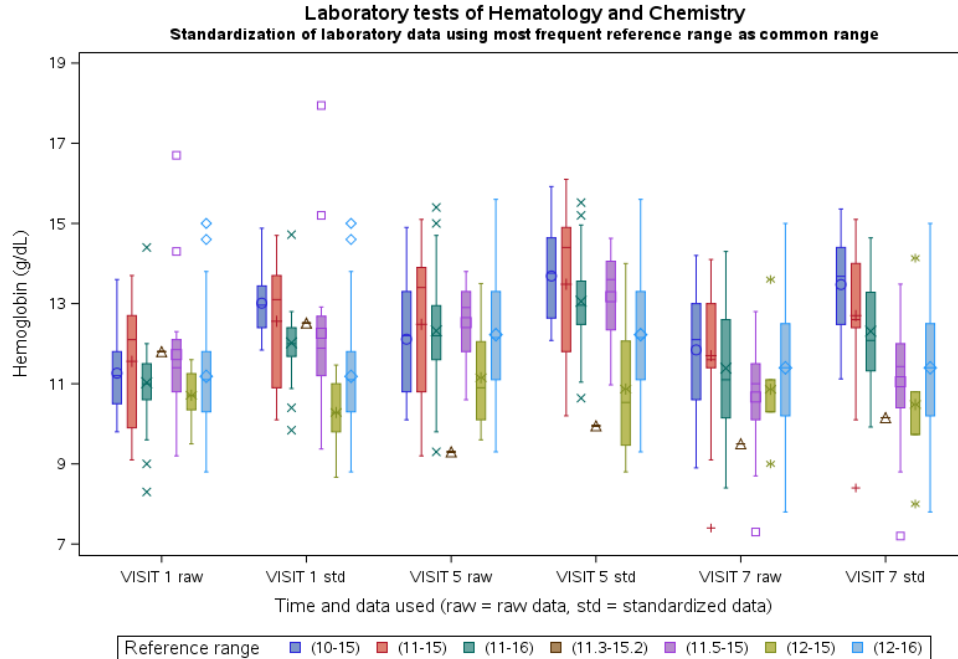
n/obs (in order of appearance): VISIT1: 19/19, 17/17, 39/39, 1/1, 15/15, 8/8, 69/69, VISIT5: 19/19, 17/17, 40/40, 1/1, 16/16, 8/8, 70/70, VISIT7: 16/16, 17/17, 36/36, 1/1, 13/13, 5/5, 66/66

Hemoglobin - Females



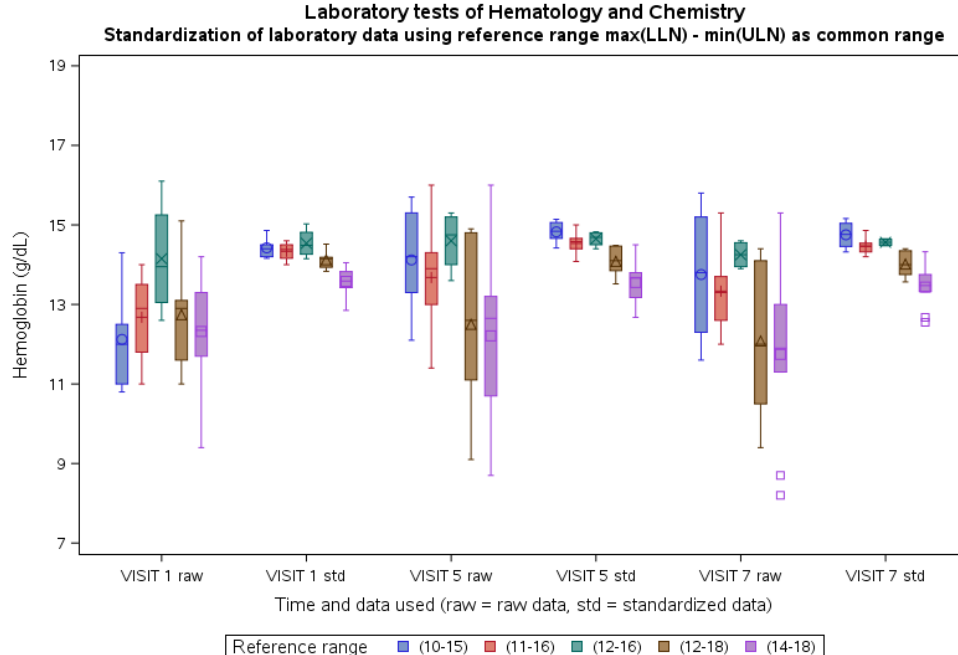
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Hemoglobin - Females



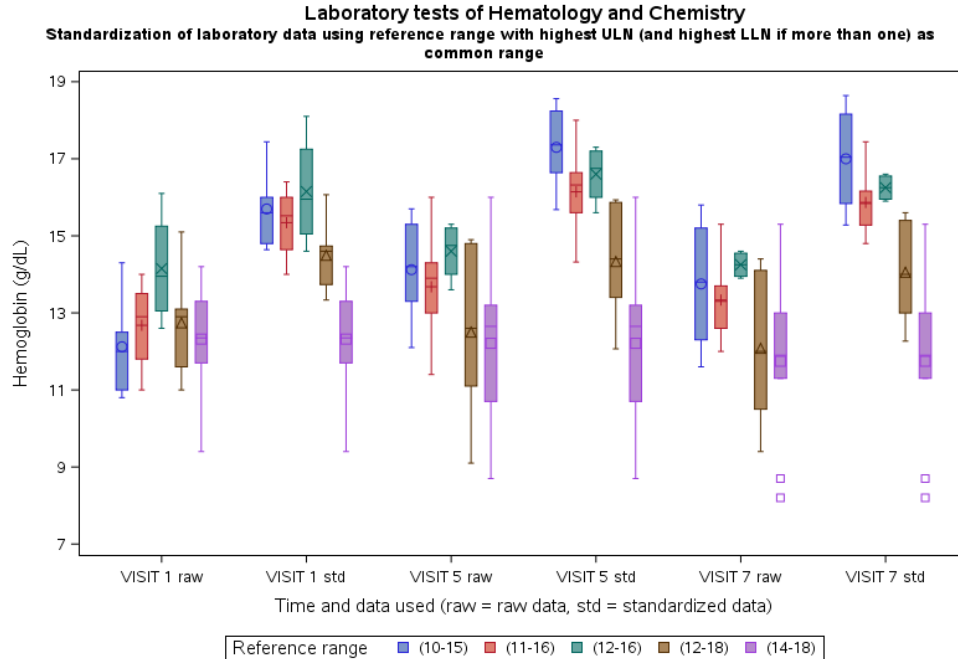
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Hemoglobin - Males



n/obs (in order of appearance): VISIT1: 5/5, 9/9, 4/4, 5/5, 10/10, VISIT5: 5/5, 9/9, 4/4, 5/5, 10/10, VISIT7: 4/4, 9/9, 4/4, 5/5, 9/9

Hemoglobin - Males



n/obs (in order of appearance): VISIT1: 5/5, 9/9, 4/4, 5/5, 10/10, VISIT5: 5/5, 9/9, 4/4, 5/5, 10/10, VISIT7: 4/4, 9/9, 4/4, 5/5, 9/9

Hemoglobin - Males

