

CLIA Waiver Statistical Issues for CBC/ADCC Devices

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Outline

- Background & terminology
- Establishing "Accuracy"
- Study conditions
- Allowable error
- Reference ranges
- Performance
- Summary

510(k) vs Waiver

- 510(k) Compare to marketed device
“Substantial equivalence”
- Waived device (WM): Compare to Comparative Method (CM)
Establish “accuracy”
- 510(k): Most CBC Assays are in hands of laboratorian
- Waiver: CBC Assay in hands of non-lab health providers

Waiver By Regulation

- Dipstick/tablet reagent urinalysis
- Fecal occult blood
- Ovulation tests
- Urine Pregnancy tests
- ESR
- **Hemoglobin (copper sulfate)**
- Blood glucose devices (FDA home use)
- **Spun microhematocrit**
- **Hemoglobin single analyte instruments**

Imprecision vs Systematic Bias

- **Most lab assays have variability:**
By running samples in duplicate and averaging you reduce variability
- **Systematic bias implies a new assay yields incorrect values on average:**
If an assay has systematic bias, it cannot be accurate. Averaging over multiple runs of same assay is not sufficient.
- **Guidance allows for assays that have negligible bias**

Traceable Method

- Method traceable to references of higher order. It can be certified reference materials, a reference measurement procedure, or a network of reference laboratories.
- Guidance allows for traceable method if reference method is unavailable.

Establishing accuracy

Manual Counts: Reference method:

- Erythrocytes (Red Blood Cells)
- Leukocytes (White Blood Cells)
- WBC Differentials:
 - 3 part: Lymphocytes, Monocytes,
and Granulocytes
 - 5 part: Granulocytes:
Neutrophils, Eosinophils, Basophils
- Platelets

Counting Cells: Comparative Method

- Manual Counts are “noisy” (imprecise)
- Sponsor may:
 - a) average over multiple manual counts or
 - b) show a well-established CBC device is traceable to manual counts:
 - i) Citing literature
 - ii) In House study
- **Reduce imprecision in CM:
Easier to pass**

One Step Design

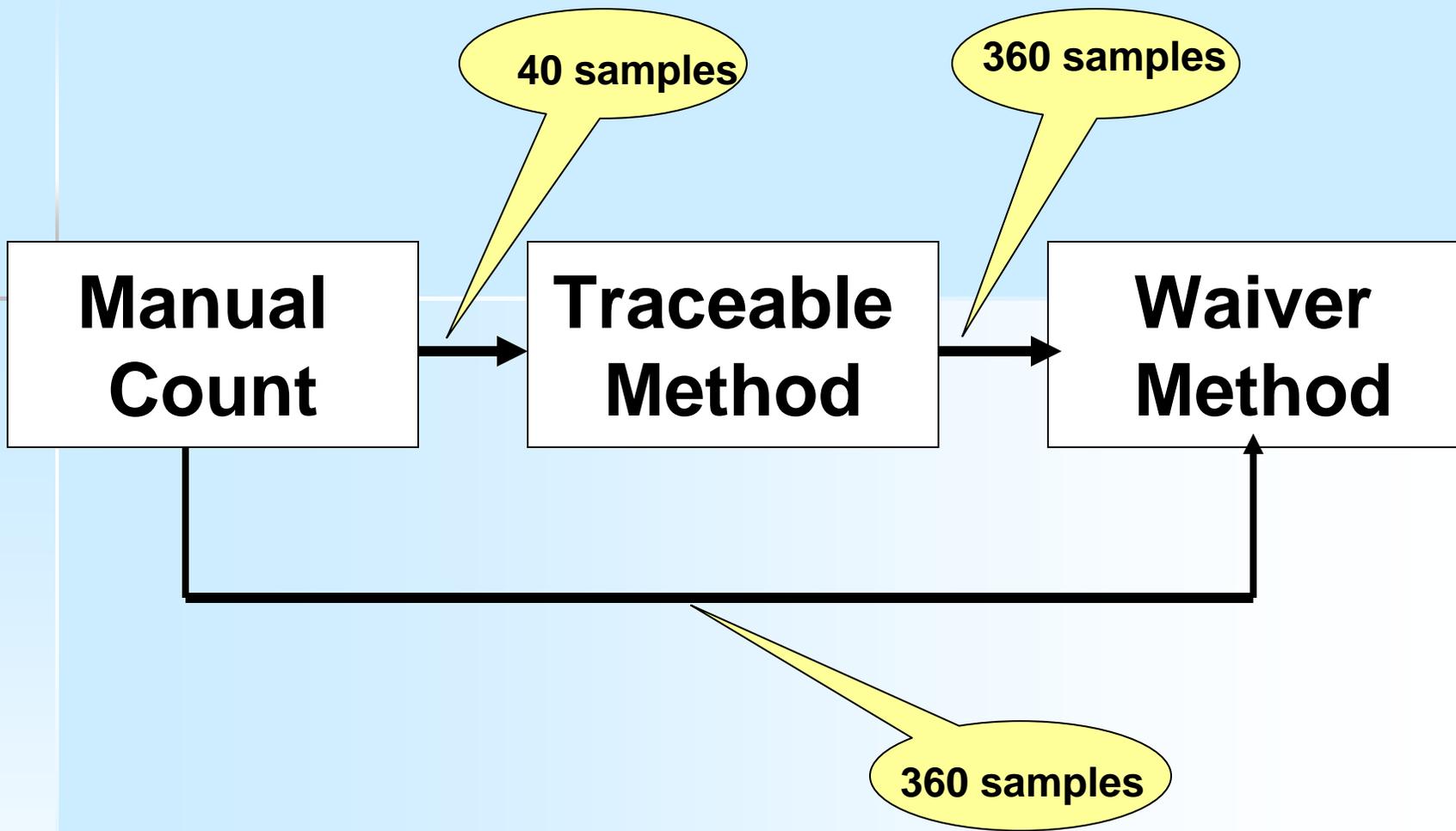
- Manual counts in duplicate, triplicate or quadruplicate (but it should be consistent across the samples) is CM
- Compare their own device (WM) result to average manual count for the same specimen.
- Very labor intensive with 360 patient specimens.

Two Step Design: Part I

- Possible Traceable method:
Lab CBC result: also subject to imprecision.
A good Lab CBC assay: negligible bias.
- Establish Traceability:
Can use literature, or do a study
- Need at least **40** samples to span the measurement range of each analyte
- Can average replicate lab CBC results (CM)
- Develop equation: Lab CBC versus Manual

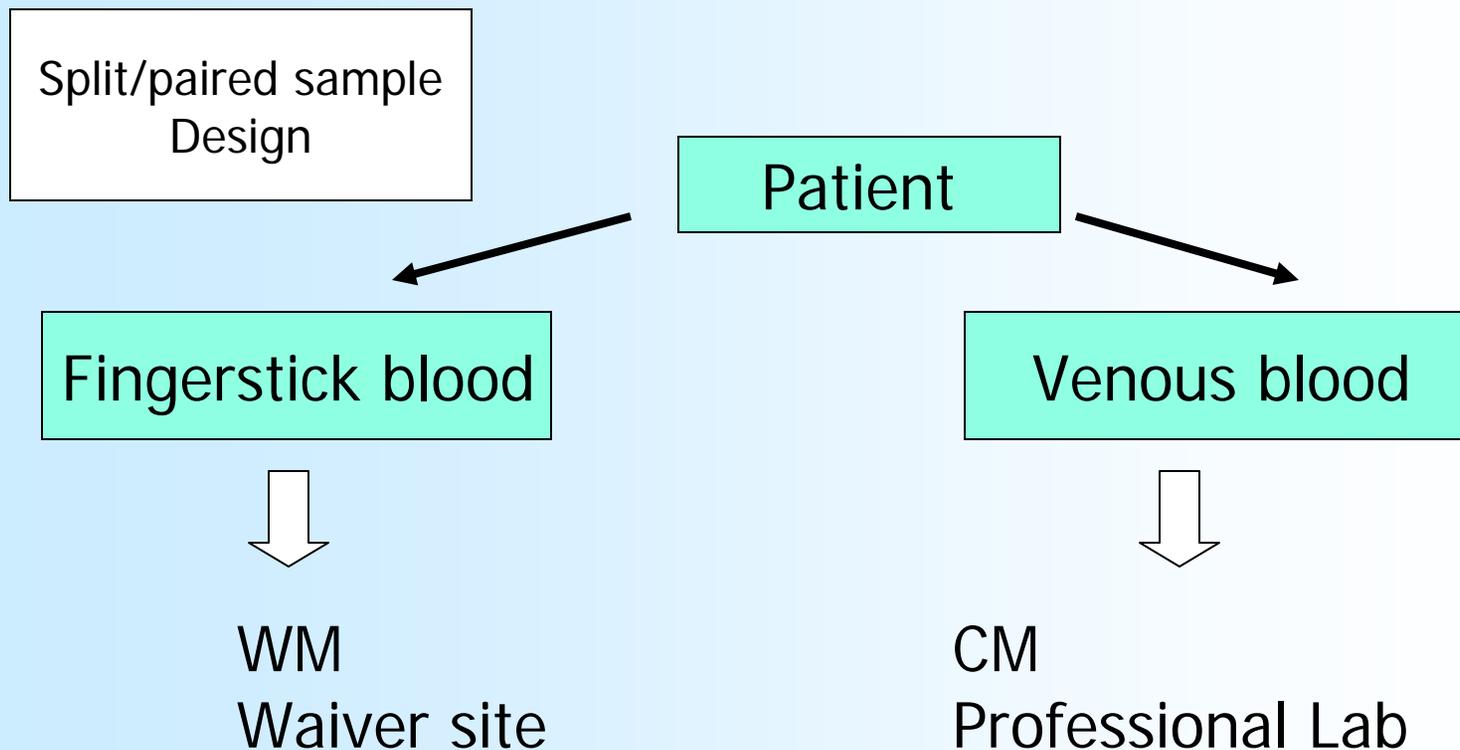
Two Step Design: Part II

- Compare Waiver (WM) result to CM
WM measured in Waiver Setting
- CM: Avg of Duplicates of Lab CBC
Counter
- Split sample goes to lab for analysis
- N=360 patient specimens



Sponsor has more than one option

Demonstrating “Accuracy” – Quantitative Study Design



Waiver study

- Should mimic real clinical conditions
 - Device use integrated into normal work
 - Study takes 2 to 4 weeks
- Should include 3 or more sites
- Should include 9 or more users with no more than 3 per site
- Users should reflect real world use
 - Not trained laboratorians

Study conditions

- User aware of safe handling of blood specimens
- Training:
 - Quick reference instructions
 - Package insert
 - 1-800 line if offered when marketed
- Training: consistent with instructions under real world use

Quality Control During Study

- Should mimic real world conditions
- Consistent with state and local requirements for CM
- QC materials need to be recommended or provided by sponsor

Study

- Specimens need to span measurement interval of device:

Consider types of study sites

- Up to 1/3 contrived, or spiked specimens
- About 120 specimens per site
- At least 360 specimens overall

Allowable Total Error

- Defined for some analytes in Guidance:

Analyte	CLIA 88 acceptable limits
Hemoglobin	$\pm 7\%$
Hematocrit	$\pm 6\%$
WBC	$\pm 15\%$
RBC	$\pm 6\%$
Platelet count	$\pm 25\%$

"Analytical Goals & State of Art"

Buttarelo and Plebani AJCP 2008 130:104-116

	CLIA88(%)	Recently Reported Ranges (International, %)
■ WBC	15	5.4-8.8
■ RBC	6	1.5-1.8
■ Hgb	7	1.2-1.9
■ PLT	25	5.2-9.8

Notes: assumes same ATE over entire range

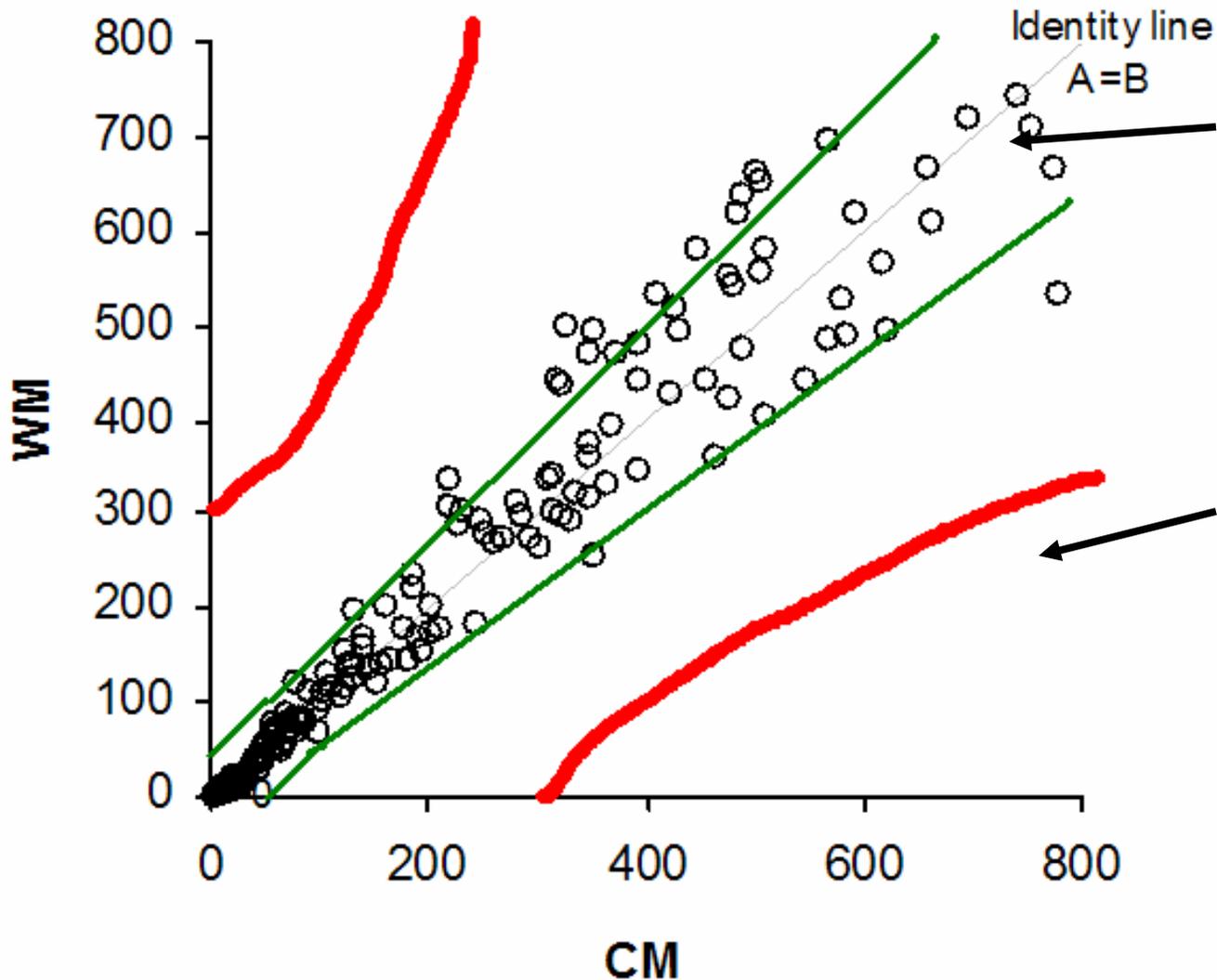
Limits of Erroneous Results

- Definition: Patient results inside the LER pose a risk to patient safety
- Concept defined in Waiver Guidance: need clinical input

Clinical Considerations with ATE and LER

- Indications and intended use populations for CBC and differential counts are heterogeneous.
- ATE and LER should be specified to meet the most demanding intended use settings.
- ATE and LER might vary across the range of reportable values.

Allowable Total Error(ATE), Limits for Erroneous Results



**Allowable
Total Error :**
(at least 95% of
subjects)

**Limits for
Erroneous
Results**
(0% of subjects).

Allowable Total Error

- White Blood Cell (WBC) differentials
- CLIA88 :
 - $\pm 3SD$ for Proficiency Testing
- Criteria not appropriate for an ATE

"Analytical Goals & State of Art"

Buttarelo and Plebani AJCP 2008 130:104-116

	Recently Reported Intervals (International, %)	ATE (%) for Waiver
Neutrophils	3.1-7.0	??
Lymphocytes	4.0-11.9	??
Monocytes (MON)	13.4-58.7	??
Eosinophils (EOS)	16.0-37.3	??
Basophils (BAS)	35.5-155.5	??

Notes: MON, EOS and BAS rarer in healthy patients: uniform ATE (%) may not be ideal

Reference intervals

- 2.5th to 97.5th percentiles of apparently healthy subjects
 - May differ by age, gender, altitude
- Establishing reference interval¹: 120 subjects
- Verifying reference interval¹: 20 subjects

How likely is establishing or verifying a reference interval in a waived setting?

¹CLSI document C28-A2

Options for Reference Intervals in Waived Settings

- Use values in 510(k): Cited references/real data
- Use values from large surveys (e.g., NHANES¹, broken down by age & sex) and or literature (e.g., textbooks²)
- Calculated using a well-established lab CBC counter

¹ NHANES III: National Health & Nutrition Examination survey, NCHS (CDC)

² Williams: Hematology (5th ed), McGraw-Hill (1995)

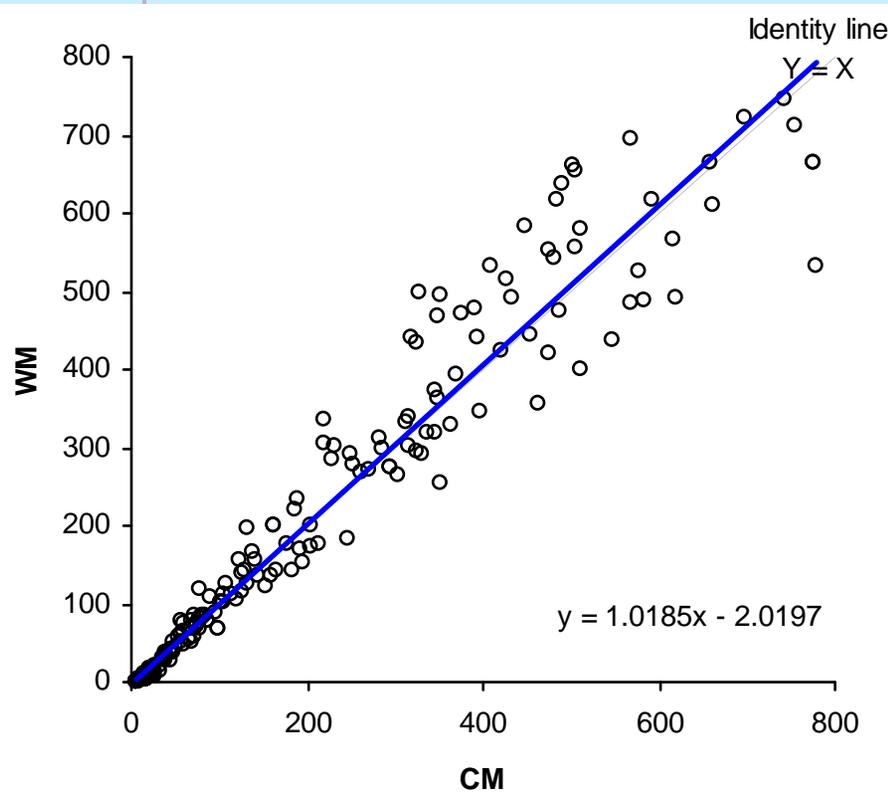
Performance

- Low, medium and high ranges for each analyte predefined
- Allowable Total Error and Limits of Erroneous Results predefined
- Samples should span measurement interval (include abnormal specimens)
- Sponsor must pass for each analyte

Performance: Part I

- **Capture bias:**
 - Plot of WM (Y-axis) vs CM (X-axis)
 - Overall
 - By site
 - By low, medium and high ranges
 - Regression analyses

Demonstrating “Accuracy” – Systematic bias



Appropriate type of regression;

$$Y = a * X + b$$

Evaluation of systematic bias at the medically important concentrations.

Negligible systematic bias

Performance: Part II

- At least 95% of WM values fall in ATE
- 95% two-sided lower Confidence Bound greater than 92%
- Similar percentages in low, medium and high ranges
- 0% of WM values fall in LER
- 95% two-sided upper Confidence Bound less than 1%

Summary

- FDA would like you to consider the following while addressing our questions:
 - What the Allowable Total Error ought to be for WBC Differentials
 - What the Limits of Erroneous Results ought to be for all CBC analytes
 - How reference intervals should be handled