Transitioning QIBs into Clinical Trials: 
Practical Implementation Requirements

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Questions:

• How can our knowledge about measurement error be used to better design clinical trials?
• What do we really need to know about the QIB?
Level 1: Technical Performance Validation

Test-Retest Studies:
- Estimate repeatability

Phantom Studies:
- Estimate bias, assess linearity

Reproducibility Studies:
- Estimate effect of imaging methods on precision and bias

Level 2: Qualification

Diagnostic Accuracy Studies:
Can QIB discriminate between health states (e.g. presence/absence of disease, staging)?

Integrated Biomarker Studies:
Is QIB associated with patient outcomes (e.g. Progression-free survival (PFS), Patient-reported outcomes (PROs))?
Example 1 (Qualification): Can ultrasound elastography discriminate subjects with liver cirrhosis (stage F4) from those without cirrhosis?

Is shear wave speed a diagnostic biomarker?
**Example 2 (Qualification):** Does the change in CT lung nodule volume after two weeks of treatment predict patient outcome?

*Is the change in CT tumor volume a potential monitoring biomarker?*

**Example 3 (Utilization):** Consider a RCT of Alzheimer’s patients, comparing accumulation of amyloid over two years in subjects undergoing a neuroprotective treatment vs. subjects being treated symptomatically.

*SUVr is used as study endpoint.*
Example 4 (Utilization): SPECT specific binding ratio (SBR) in the posterior putamen is used as an eligibility criterion for identifying Parkinson’s disease subjects likely to benefit from a new intervention.

*SBR is used as a selection biomarker.*

How does QIB measurement error affect clinical trials?

1. Attenuates ability of biomarker to discriminate between health states or predict outcome
   - Less power (not able to qualify the QIB)

2. Leads to incorrect decisions
   - Misinterpret measurements or change in measurements (not able to utilize the QIB)
How does QIB measurement error affect clinical trials?

1. Attenuates ability of biomarker to discriminate between health states or predict outcome
   - Less power (not able to qualify the QIB) re-calculate sample size, accounting for QIB’s measurement error

2. Leads to incorrect decisions
   - Misinterpret measurements or change in measurements (not able to utilize the QIB) use the QIB measurement to construct 95% CI for true value

Correction to Sample Size:

\[ \text{# patients needed} = N_X \left( \hat{\beta}_1^2 \hat{\sigma}_D^2 + \hat{\sigma}_\epsilon^2 \right) / \hat{\beta}_1^2 \hat{\sigma}_D^2 \]

sample size if there was no measurement error

Obuchowski et al, JNCI in press
Correction to Sample Size:

\[ \text{# patients needed} = N_x \left( \hat{\beta}_1^2 \hat{\sigma}_b^2 + \hat{\sigma}_\epsilon^2 \right) / \hat{\beta}_1^2 \hat{\sigma}_b^2 \]

regression slope of measurements on true values
(we often assume slope=1 but critical that we test that)

Obuchowski et al, JNCI in press

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between-subject variance

Obuchowski et al, JNCI in press
Correction to Sample Size:

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within-subject variance
(from test-retest studies)

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95\% CI for the true value (to account for measurement error):

\[ \left( Y_i - \hat{\beta}_0 \right) / \hat{\beta}_1 \pm 1.96 \times \hat{\sigma}_\epsilon / \hat{\beta}_1 \]

fixed (mean) bias

Obuchowski et al, JNCI in press
95% CI (to account for measurement error):

\[
\frac{Y_i - \hat{\beta}_0}{\hat{\beta}_1} \pm 1.96 \times \frac{\hat{\sigma}_e}{\hat{\beta}_1}
\]

regression slope of measurements on true values

Obuchowski et al, JNCI in press

95% CI (to account for measurement error):

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\]

test-retest SD

Obuchowski et al, JNCI in press
**Qualification Example:** Consider a clinical trial of a new therapeutic intervention for lung cancer.

**Primary objective:** Compare progression free survival (PFS) of subjects in new vs. standard trt

**Secondary objective:** Test if change in CT lung nodule volume after two weeks predicts PFS in smaller subpopulation.
QIBA profile for CT tumor volume change in advanced disease:

wCV~8.5% for tumors with longest diameter 50-100mm
- *this allows different scanners and readers at two time points*

Ignoring measurement error, **N=54** subjects would be accrued to construct 95% CI of width ±0.3 for hazard ratio.

Accounting for wCV=8.5% and slope=1, we need to recruit **N=62**.
Trade-off between level of standardization and study practicality

<table>
<thead>
<tr>
<th>Quantitative Assessment</th>
<th>Qualitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same scanner, Same reader, Same analysis tool</td>
<td>Same scanner, Different reader, Same analysis tool</td>
</tr>
<tr>
<td><strong>wCV</strong></td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Study Power</strong></td>
<td>~80%</td>
</tr>
</tbody>
</table>

* A sample size of N=54 is needed when no measurement error is present for 80% power, 5% type I error to detect a HR>1.

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**Utilization Example:** SPECT specific binding ratio (SBR) in the posterior putamen used as eligibility criterion for Parkinson’s trial.

- **SBR < 1.2** → eligible for study (likely to benefit from new trt)
- **SBR > 1.2** → excluded from study (unlikely to benefit)
QIBA’s Profile on quantifying dopamine transporters with $^{123}$Iodine-labeled ioflupane

1. SPECT SBR measurements have wCV=15%
2. Regression slope ~ 1.0

Furthermore, assume negligible fixed (mean) bias.

**Protocol A:** Ignore measurement error and enroll patients if SBR $< 1.2$

**Protocol B:** Use our knowledge of the technical performance of SBR measurements to construct 95% CI for true value. Enroll patients if CI for true value suggests they are eligible.
Conclusions: *Implementing QIBs in Clinical Trials*

1. Ignoring measurement error leads to:
   - low power in clinical trials
   - misinterpretation of QIB measurement
Conclusions: Implementing QIBs in Clinical Trials

1. Ignoring measurement error leads to:
   - low power in clinical trials
   - misinterpretation of QIB measurement

2. If you know the measurement error:
   - recalculate sample size
   - use 95% CI for true value instead of QIB measurement
   - assess trade-off between standardization and practicality

Implementing QIBs in Clinical Trials

For Qualification studies, we need to know:
   - test-retest variance (wSD, wCV)
   - linearity exists and magnitude of slope

   - reproducibility (to assess trade-off in standardization/practicality)

For Utilization studies, we also need to know:
   - mean (fixed) bias