

AI-700 and Diagnostic Imaging Performance Characteristics

Cardiovascular and Renal Drugs
Advisory Committee
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Outline

- Trial Design
- Critique of Performance Characteristics
(Sensitivity / Specificity / Accuracy)
- Criteria for Non-Inferiority Studies
- Trial Results
- Conclusions

AI 700 Clinical Trials Design

- Two Single Arm Cross-Over Non-Inferiority trials
- SOR : Angiography when available (42% for Study 32 and 94% for Study 33); otherwise Clinical Assessment
- SOR determined Disease Prevalence:
44% in Study 32 and 58% in Study 33
- Diagnosis: Patient level (Disease/No Disease)
- Concordance of diagnosis between Images and the SOR did not require localization of disease

AI 700 Clinical Trials Design (Continued)

- Comparator: SPECT Imaging
- Endpoints : Accuracy, Sensitivity and Specificity
- Hypotheses: For each endpoint
 - H_0 : Risk Ratio (Echo/SPECT) \leq NI margin
 - H_1 : Risk Ratio (Echo/SPECT) $>$ NI margin
- Success Criteria: The lower limit of the 95% confidence interval for the Risk Ratio must exceed the NI margin simultaneously for two out of the 3 readers for all three endpoints.

Sensitivity/Specificity/Accuracy

- Sensitivity / Specificity (but not Accuracy)
 - Are independent of disease prevalence
 - Provide true positive/negative rates in patients with/without disease
 - Impact the pretest probability of disease
- Accuracy provides only a “correctness” rate
 - Doesn't distinguish among various Sensitivity and Specificity levels

Limitations of Accuracy

- Example#1: Disease Prevalence = 0.5
- Risk Ratio Threshold set at NI = .87
- Acceptable New Test Accuracy and Specificity
- Unacceptable New Test Sensitivity

	New Test	Old Test	Ratio New/Old
Sensitivity	60%	80%	0.75
Specificity	70%	70%	1.0
Accuracy	65%	75%	0.87

Limitations of Accuracy (continued)

- Study 32: Disease Prevalence = 0.4
- Risk Ratio Threshold set at NI = .87
- Acceptable New Test Accuracy and Specificity
- Unacceptable New Test Sensitivity
- Values are Averages over Readers

	New Test	Old Test	Ratio New/Old
Sensitivity	61%	78%	0.78
Specificity	74%	64%	1.16
Accuracy	68%	70%	0.97

Limitations of Accuracy (continued)

- Study 33: Disease Prevalence = 0.6
- Risk Ratio Threshold set at NI = .87
- Good New Test Accuracy and Sensitivity
- Marginal New Test Specificity
- Values are Reader Averages

	New Test	Old Test	Ratio New/Old
Sensitivity	71%	61%	1.16
Specificity	64%	76%	0.84
Accuracy	69%	67%	1.03

Non-Inferiority Design Elements (Acceptable Comparator Performance)

- Comparator (SPECT) historical performance
 - From ACC guidelines:
 - SPECT Sensitivity: mean = 89%
 - SPECT Specificity: mean = 75%

- Agency recommendation:
 - SPECT should achieve a minimal performance level in the trials with Sensitivity $\geq 82\%$ and Specificity $\geq 66\%$
 - These numbers are 3σ 's lower than the ACC guidelines

- Sponsor's Pre-specified SPECT Minimum performance levels
 - Sensitivity $\geq 76\%$ and Specificity $\geq 59\%$

Non-Inferiority Design Elements (Non-Inferiority Risk Ratio Margin)

- FDA recommended Non-Inferiority Margins
 - Sensitivity $> .87$
 - Specificity $> .85$
- Sponsor's Pre-specified Non-Inferiority Margin
 - Accuracy
 - Sensitivity
 - Specificity

} > 0.83

Consequences of Margin Choices

SPECT VALUE	MINIMAL ECHO VALUES FOR R = .83		MINIMAL ECHO VALUES FOR R = .87	
	ECHO	SPECT - ECHO	ECHO	SPECT - ECHO
.60	.50	.10	.52	.08
.70	.58	.12	.61	.09
.80	.66	.14	.70	.10
.90	.75	.15	.78	.12

Concerns on Trial Execution

- Un-blinding and Analysis of Study 32 while Study 33 was in progress
- Low Echo sensitivity observed in Study 32
- Sponsor scrapped the existing (blinded) Image reads in Study 33
- Sponsor re-trained Study 33 readers for greater sensitivity
- After re-training Study 33 Readers re-read the existing images
- Primary analysis of Study 33 is based on the re-read

Table of Performance Characteristics

	STUDY#32					STUDY#33				
Accuracy (N = 285)	R1	R2	R3	SPECT	Accuracy (N = 377)	R1	R2	R3	SPECT	
	.66	.67	.71	.70		.66	.70	.70	.67	
Ratio CI Lim	.86	.87	.93		Ratio CI Lim	.89	.96	.96		
Sensitivity (N =125)	R1	R2	R3	SPECT	Sensitivity (N = 220)	R1	R2	R3	SPECT	
	.77	.57	.50	.78		.73	.68	.73	.61	
Ratio CI Lim	.88	.63	.54		Ratio CI Lim	1.1	1.0	1.1		
Specificity (N = 160)	R1	R2	R3	SPECT	Specificity (N = 157)	R1	R2	R3	SPECT	
	.58	.75	.88	.64		.55	.72	.66	.76	
Ratio CI Lim	.78	1.0	1.2		Ratio CI Lim	.62	.84	.76		

Results

- Minimal Comparator Performance: SPECT performance met Sponsor's pre-specified minimum performance criteria for Specificity, but NOT for Sensitivity
- Risk Ratio Results: No two readers simultaneously met the Sponsor's Non-Inferiority Risk Ratio Margin for Sensitivity and Specificity in either of the studies
- All readers met the Sponsor's pre-specified Non-Inferiority Margin for Accuracy in both studies

Conclusions

- Accuracy alone is not acceptable as the sole primary endpoint in imaging studies
- Studies did not meet the Sponsor's pre-specified Risk Ratio criteria for Sensitivity and Specificity
- Inconsistency of SPECT performance levels from trial to trial (especially Sensitivity) compromises the validity of the Non-Inferiority design.