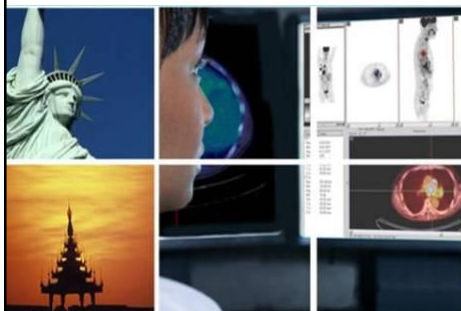


Blinded Central Review and Local Review for Progression Free Survival: The Cost of Central Audits as a Cost Saving Alternative




David Raunig, Ph.D.
ICON Medical Imaging

Historical Interest Imaging in Oncology Clinical Trials

- **Clinton-Kessler Oncology Initiative (1996)**
 - Tumor shrinkage for efficacy
 - Change in Attitude due to focus on rigor
- **Consensus to Independent Reader Teams**
 - Consensus: The Loudest Voice in the Room
 - Reader variability
 - Reader monitoring for performance
- **Local to Central Review**
 - Concern with site bias
 - Incidents of data manipulation


Recent Interest in Local Evaluations



- **Cost Reduction**
 - Site use of pro bono radiology reads
 - Burden of dealing with ICROs
- **Equivalence of local and central readers**
 - Meta-analysis → apparent equivalent results
 - No apparent effect from increased variability
- **Reader variability**
 - Central reads variability measurements
 - High reader discordance casts doubt on data quality


Society for Clinical Trials 2013 21 May 20123 3

Presentation Outline



- **Background**
 - Review of Central read process and Reader performance
 - Summary of central read issues
- **Motivation for critical review of LE**
- **Review of the Data used to justify LE reads**
- **Cost of Local Evaluation Audits**
 - Budget
 - Data Quality
 - Sponsor Burden
- **Conclusions and Recommendations**


Society for Clinical Trials 2013 21 May 20123 4

 A Symbol of Excellence

Imaging Endpoints and Radiological Reads

- **The Reader as a measurement instrument**
 - Validation
 - Calibration
- **Central Review**
 - Two Primary Readers per patient
 - Well and equally trained
 - One Adjudicator
 - Protects against undo influence
 - Monitors and assesses performance of the other readers
 - Form 1572 Completed for each reader
- **Local Evaluation**
 - One Primary Reader per timepoint (possibly per patient)
 - Training is done for most study radiologists
 - Form 1572 typically not completed for each reader
 - Many readers protect against the undo influence


Society for Clinical Trials 2013
21 May 20123
5

 A Symbol of Excellence

Read Protocols in Clinical Trials

- **Date of Progression**
 - Disagreement settled by adjudicator
- **Confirmation of Progression**
 - Central reader(s) will confirm progression for those patients progressed by the local reader
 - Does Central Readers agree with progression
 - Non-progressed patients are not typically read centrally
- **Collect and Hold**
 - Images are collected and archived
 - No central read conducted unless local evaluation failed
 - 16 studies found internally at ICON Medical Imaging


Society for Clinical Trials 2013
21 May 20123
6



Review of Meta Analysis of Local versus Central Readers

What was actually evaluated in the 27 studies

Society for Clinical Trials 2013 21 May 20123 7




Meta Analysis Study Background

- **Background**
 - 27 studies involving local and central readers were reviewed to compare hazard ratios and agreement
 - Results:
 - HR comparison → equivalent on average (slope \approx 1)
 - High correlation → $r = 0.947$
- **Assumptions:**
 - Local and Central reads were independently conducted
 - Local and Central reads were on identical data
 - Representative sample of all clinical trials


Society for Clinical Trials 2013 21 May 20123 8

Actual Profile of LE versus ICR Studies presented at ODAC	
Type of Comparison	Number of Studies
Independent comparison of completed reads Local and BICR	4
Possible Independent	2
Independent Comparison 1 Primary Central Reader	1
Academic v BICR	1
Confirmation of Progression	5
Suspected Confirmation of PD	2
Shared information	3
Included Other progression criteria	2
Unknown	7

Society for Clinical Trials 2013 21 May 20123 9

Analysis of Cost Benefit of Audit Methodology of Local Evaluations	
	

Cost Analysis of Independent Audit Methodology




ICON
A Symbol of Excellence

- **Motivation**
 - Local evaluation studies seem like they would be cheaper
 - Central Review: “unnecessary expense”
 - Local Evaluation: “gains in efficiency and cost”
 - No quantification of the savings
- **Cost Basis for Analysis**
 - 7 internal completed studies
- **Analysis Assumptions**
 - No increases investigator costs
 - Phase III
 - N=700
 - Total / CRO cost - \$100M / \$2.3M
 - 100% collect and hold / random selection of 30% for audit
 - 16% Probability of complete central read (Dodd 2011)
 - Other costs constant

Society for Clinical Trials 2013 21 May 20123 11

Preliminary Cost Analysis Results




ICON
A Symbol of Excellence

	Cost Savings (Audit) / (Complete Read)	
	(2 P + 1 A) / (2 P + 1 A)	(1 Primary) / (2P+1A)
No central read needed	22% (~\$535k)	10% (~\$240k)
Central read needed	18% (~\$440k)	8% (~\$160)
Overall Expected Cost Savings	\$520k	\$226k


Society for Clinical Trials 2013 21 May 20123 12

Other Costs Not Considered




- **The cost of increased reader heterogeneity**
 - Example – FDA Briefing Document – Yondelis Study of Ovarian Cancer
 - ICR – ICR discordance rate = 39%
 - ICR – LE discordance rate = 63%
 - Example: ICON Collect and Hold NSCLC
 - ICR– ICR Discordance rate = 51%
 - ICR– LE Discordance rate = 57%
- **Site Radiology contracting**
- **Prepare individual sites to comply with FDA standards.**
- **Cost of implementing an LE Audit**
- **Delays**
- *Note: A minor problem in unconsidered costs would quickly negate a \$240k cost savings*

Society for Clinical Trials 201321 May 2012313



Cost to Data Quality


A Symbol of Excellence

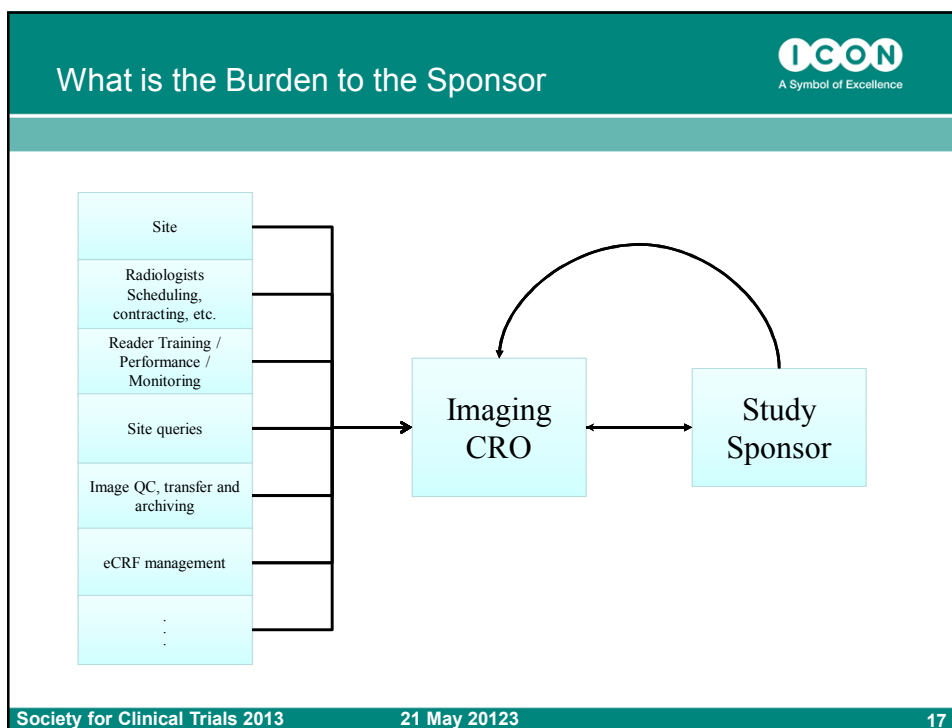
Data Quality Cost of Going to Local Evaluations

- **Loss of any ability to monitor reader performance**
 - Reader adjudication rate is not available
 - Still exists, just not measured
 - Example:
 - An unknown 63% Adjudication Rate would not be a concern
 - A known 39% Adjudication Rate would generate actions
 - Option: Training and monitoring
- **Loss of source data / Significant site delays in delivery**
 - Evidence in the literature
 - LE evaluated images not delivered to IRC, even at the end of the study
 - Anecdotal experience shows that up to 40% of the source data is not available


Society for Clinical Trials 201321 May 2012315


A Symbol of Excellence

Cost of ICRO Burden to the Sponsor



Conclusions



- **Equivalence** has not been sufficiently demonstrated from the literature
- **Failed local evaluations** were not included in the meta analysis though they exist in ICRO archives
- **A 10% cost savings** when a fair cost comparison of read paradigms done
 - A more complete analysis is in progress
- **Incorrect inference for undo burden** from the ICRO
 - Did not consider upstream effects that would still exist without the ICRO
- **Audits should be carefully discussed** with the ICRO statistician to minimize possible additional costs
- **Training of Site Radiologists** by qualified instructors is necessary to reduce variability and critical when an indication is difficult to assess
- **Tumor Response has not been evaluated** for local evaluation and the role of local evaluation for PFS and central readers for response must be predetermined

Society for Clinical Trials 2013 21 May 20123 18

Recommendations

- **Include all stakeholders** in any future discussions of the use of audits or site monitoring
- **Conduct a retrospective analysis** of local and central reader performance with all stakeholders involved in the design.
- **Complete a valid cost comparison** to provide study sponsors with valid cost information.
- **Reduce reliance on adjudication rate** as a measure of data quality.

Society for Clinical Trials 2013
21 May 20123
19

References

- Amit O, Mannino F, Stone AM, Bushnell W, Denne J, Helterbrand J, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer. 2011;47(12):1772-8.
- Dodd LE, Korn BF, Jaffe CC, et al: Blinded independent central review of progression-free survival in phase III clinical trials: Important design element or unnecessary expense? J Clin Oncol , 200826:3791-3796
- Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. An Audit Strategy for Progression-Free Survival. Biometrics. 2011;67(3):1092-9.

Society for Clinical Trials 2013
21 May 20123
20

Acknowledgements



- **ICON Medical Imaging**
 - James Conklin, MD.
 - Greg Goldmacher, MD. Ph.D.
 - Ninad Mantri, MS