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

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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

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
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

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
Review of Meta Analysis of Local versus Central Readers

What was actually evaluated in the 27 studies

Meta Analysis Study Background

• Background
  – 27 studies involving local and central readers were reviewed to compare hazard ratios and agreement
  – Results:
    • HR comparison \(\rightarrow\) equivalent on average (slope \(\approx\) 1)
    • High correlation \(\rightarrow\) \(r = 0.947\)

• Assumptions:
  – Local and Central reads were independently conducted
  – Local and Central reads were on identical data
  – Representative sample of all clinical trials
Actual Profile of LE versus ICR Studies presented at ODAC

<table>
<thead>
<tr>
<th>Type of Comparison</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent comparison of completed reads</td>
<td></td>
</tr>
<tr>
<td>Local and BICR</td>
<td>4</td>
</tr>
<tr>
<td>Possible Independent</td>
<td>2</td>
</tr>
<tr>
<td>Independent Comparison</td>
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</tr>
<tr>
<td>1 Primary Central Reader</td>
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<tr>
<td>Academic v BICR</td>
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<tr>
<td>Confirmation of Progression</td>
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</tr>
<tr>
<td>Suspected Confirmation of PD</td>
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</tr>
<tr>
<td>Shared information</td>
<td>3</td>
</tr>
<tr>
<td>Included Other progression criteria</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
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</tbody>
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Analysis of Cost Benefit of Audit Methodology of Local Evaluations
Cost Analysis of Independent Audit Methodology

- **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

### Preliminary Cost Analysis Results

<table>
<thead>
<tr>
<th>Cost Savings (Audit) / (Complete Read)</th>
<th>$</th>
<th>$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2 P + 1 A) / (2 P + 1 A)</td>
<td>22% (~$535k)</td>
<td>10% (~$240k)</td>
</tr>
<tr>
<td>Central read needed</td>
<td>18% (~$440k)</td>
<td>8% (~$160)</td>
</tr>
<tr>
<td>Overall Expected Cost Savings</td>
<td>$520k</td>
<td>$226k</td>
</tr>
</tbody>
</table>
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

Cost to Data Quality
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

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Cost of ICRO Burden to the Sponsor
What is the Burden to the Sponsor

- Site
- Radiologists Scheduling, contracting, etc.
- Reader Training / Performance / Monitoring
- Site queries
- Image QC, transfer and archiving
- eCRF management
- ...

Imaging CRO → Study 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
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.

References


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