A Sample-based Approach for Independent Review of PFS using Differential Discordance

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Presented on behalf of the PFS Independent Review Working Group

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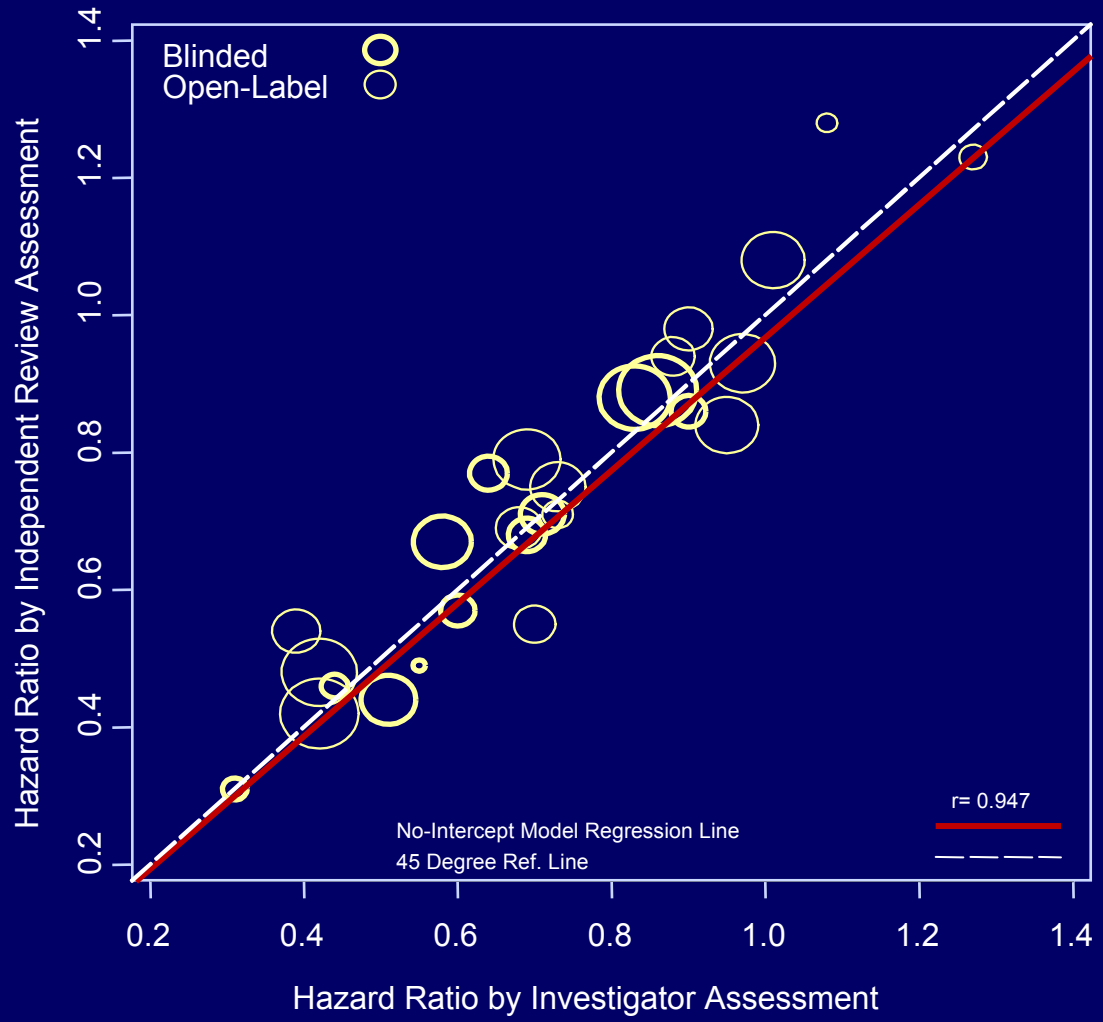
Key Points

- Local evaluation (LE) and blinded independent central review (BICR) provide comparable estimates of Tx effect in the great majority of clinical trials
- BICR is a mechanism for auditing the quality and reliability of the LE in the rare cases where evaluation bias may be present
- Desirable to lower the significant resource burden associated with a BICR by developing methods for detecting evaluation bias based on a sample of patients within the trial
- Differential discordance is an effective tool for assessing evaluation bias in a sample-based procedure

Introduction

- PFS working group formed in June 2008
- Meta-analysis undertaken to evaluate concordance in estimates of Tx effect between BICR and LE across multiple solid tumors
- Results from meta-analysis were used to motivate and develop methodology for a sample-based BICR
- Sample-based BICR developed and validated through statistical simulation
- Key findings published in European Journal of Cancer (Amit, 2011)

Results of Meta-analysis of 27 Solid-tumor trials



Ratio of BICR HR to LE HR (95% CI): 1.02 (0.96,1.07)

Defining Discordance

- **Discordance**
  - **Disagreement at the patient level between LE and BICR regarding either the occurrence or timing of progression**
- **Discordance rate**
  - **The rate at which disagreements occur on occurrence or timing of progression within a treatment arm**
- **Differential Discordance (DD)**
  - **The difference between Tx arms in discordance rates**
- **Measures of discordance can be defined in multiple ways**
  - **Some more useful than others**

BICR and Discordance

- The goal of any independent review is to confirm the Tx effect:
  - Highly concordant estimates of Tx effect are observed in the presence of significant discordance at the patient level

- Discordance is a consequence primarily of measurement error but can also be induced by evaluation bias

Discordance and evaluation bias

- **Separating evaluation bias from measurement error is critical**

- **Mechanism for evaluation bias**
  - **Investigator systematically calls progression earlier (or later) on one arm relative to other**
  - **Leads to different discordance patterns/rates in the experimental and control arms: Differential Discordance**

Defining and Evaluating Discordance

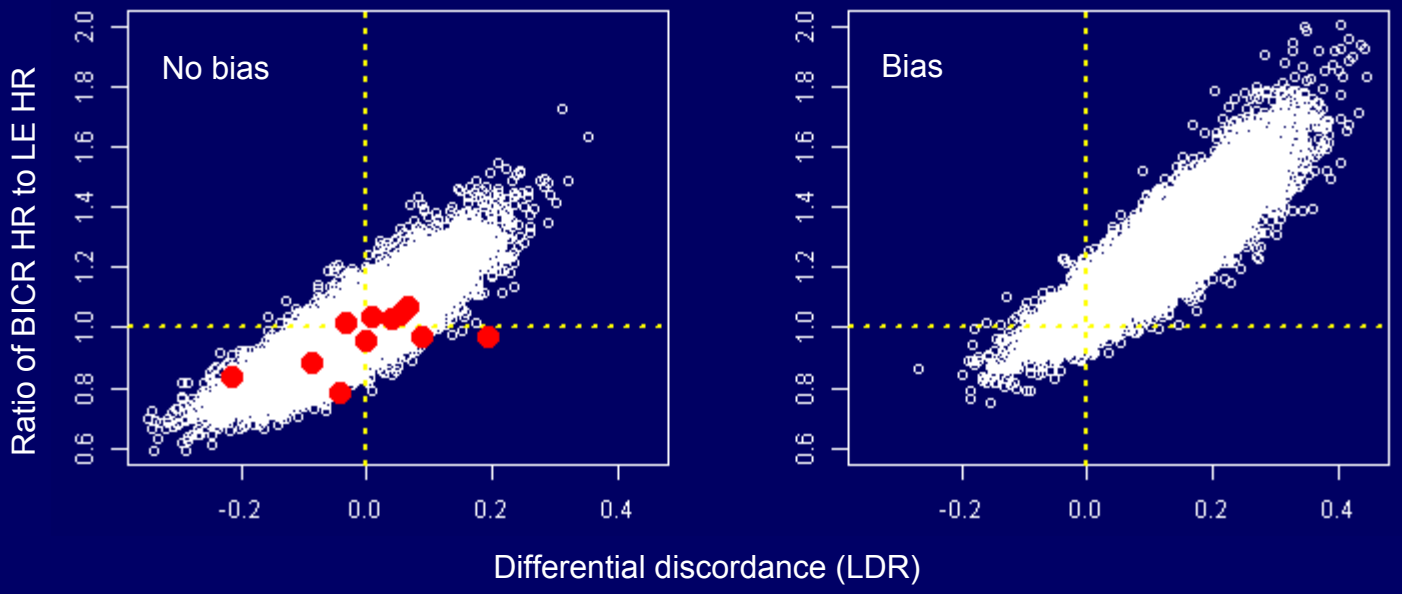
		BICR	
		PD	No PD
LE	PD	a=a1+a2+a3	b
	No PD	c	d

a1= # of times agreed on timing and occurrence of progression
a2= # of times agreed on PD event but BICR has earlier time
a3= # of times agreed on PD event but LE has earlier time

Early Discrepancy Rate: EDR (**b/(a+b)**)
Rate that LE assessed PD is called earlier than BICR PD

Late Discrepancy Rate: LDR (**(a2+c)/(a2+b+c)**)
Proportion of disagreements where LE PD's occur later than BICR PD.

Correlation between Differential Discordance and Differences in HR between BICR and LE

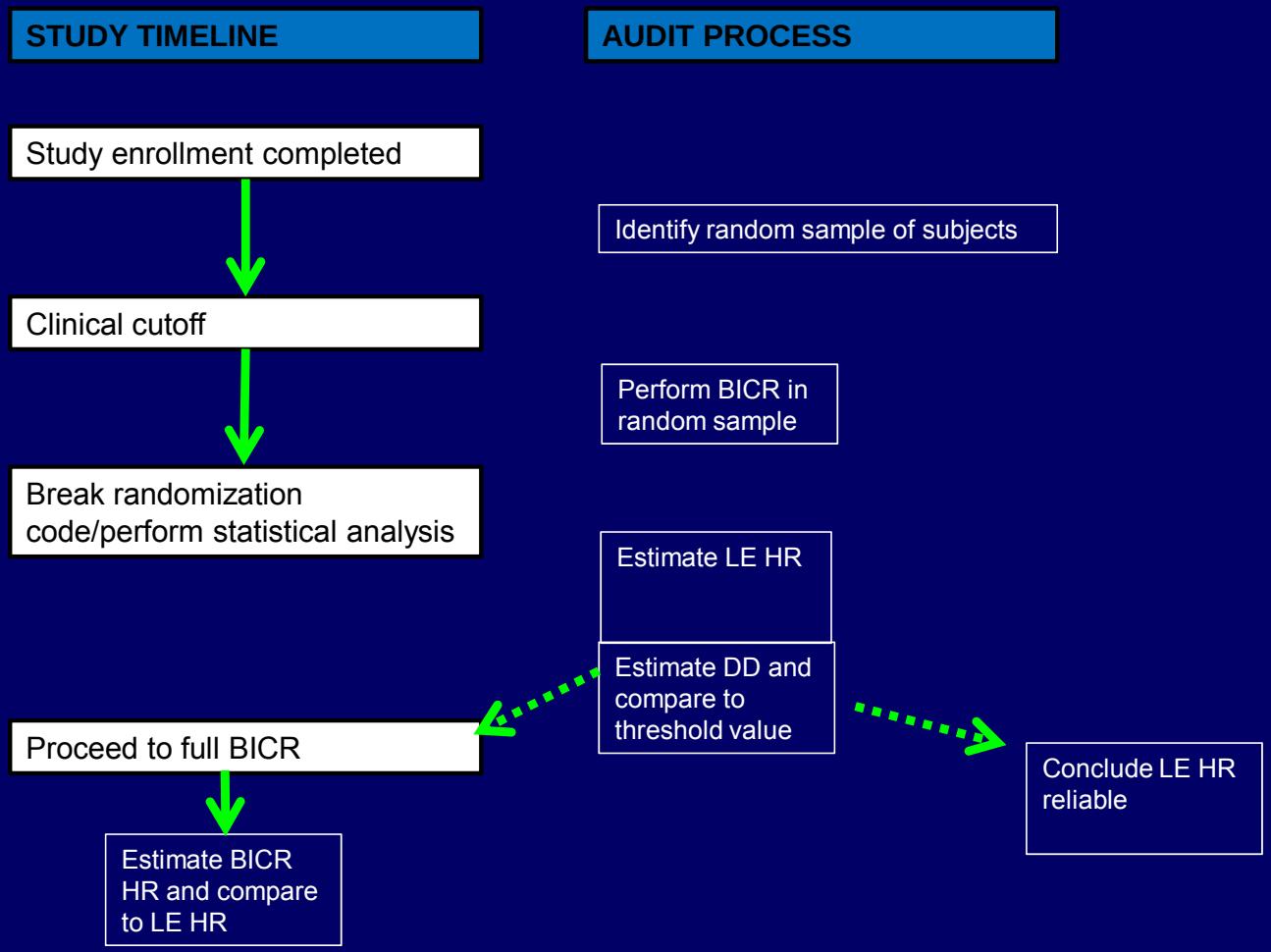


BICR as an Audit of LE using a Sample-based Procedure

- Goal of Sample-based Procedure
  - Increase confidence in integrity of trial and trial endpoints
  - Not intended to re-estimate treatment effect

- Key concepts supporting audit methodology:
  - Historically local evaluation provides reliable estimates of treatment effect
  - Want to reduce the burden of BICR while retaining a mechanism for detecting meaningful bias in the estimates of Tx
  - Meaningful bias in the estimates of treatment effect manifests as differences between treatment arms in discordance rates as measured by EDR/LDR

Audit Methodology: Sample-based Procedure



Operating Characteristics

- **Amit (2011)**
  - **Sensitivity: Probability of detecting bias in sample when it is truly present irrespective of outcome in full case review**
  - **Specificity: Probability of declaring LE reliable based on sample when no bias is present irrespective of outcome in full case review**
  - **Fixed threshold value regardless of sample size**

- **Per feedback from EMA define operating characteristics relative to the current practice for detecting evaluation bias**
  - **Comparison of hazard ratios from full case review**
  - **Relative difference of ~25% between LE and BICR HR's**
  - **Allow threshold value to reflect varying levels of uncertainty**

Sensitivity and Specificity of Procedure

		Full Case Review	
		Concordant HR	Discordant HR
Audit	DD> threshold	w	x
	DD < threshold	y	z

"Sensitivity" (positive agreement) (x/x+z): *What proportion of the time do we detect evaluation bias in the audit given you would have detected it in the full case review?*

"Specificity" (negative agreement) (y/w+y): *What proportion of the time do we conclude LE is reliable based on DD in the audit given a similar conclusion based on HR's from the full case review*

Sample-size and Threshold Values for Audit

- Threshold value based on fixing sensitivity for detecting bias at >90% for a given sample size
- Threshold value is Sample-size dependent
- Depending on desired specificity, sample sizes of 100-200 subjects are needed

Operating Characteristics: Based on 10,000 Simulations

Metric	Sample-size	Specificity	Sensitivity	Threshold value
LDR	100	61.0%	89.7%	0.0143
	150	74.9%	89.7%	0.0557
	200	86.0%	89.7%	0.0866
EDR	100	45.6%	89.7%	0.0453
	150	58.7%	89.7%	0.0153
	200	68.9%	89.7%	-0.0024

When Should a Sample-based BICR be Done

- No BICR
  - Truly blinded trials
- Sample- based BICR (Audit)
  - Open-label trials
  - Trials where complete blinding is not possible
- 100% BICR
  - Trials with smaller sample size where audit is not feasible
  - Trials where there is a strong need to increase confidence in the LE of PFS (e.g. in tumors where RECIST criteria may be more difficult to apply)

Summary and Next Steps

- **Conclusions**
  - Local evaluation consistently provides reliable estimate of Tx effect
  - Differential Discordance is a useful tool for detecting evaluation bias
  - Differential Discordance can be used to design audits of a manageable size with good operating characteristics
- **Next Steps**
  - Retrospective application of audit procedure in completed clinical trials
  - Regulatory acceptance