More about BICR – some technical concepts

Disclaimer

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Bias Reduction and Detection using BICR

- **Evaluation bias in LE may lead to estimation bias**
  - Evaluation bias may be introduced by the subjective aspect of the disease evaluation in PFS
  - When patients and investigators are unblinded to treatment assignment, PD may be declared earlier in one arm than the other in a systematic fashion
- **PFS estimated from BICR data has less evaluation bias**
  - PFS based on BICR can be the primary analysis
  - PFS based on BICR can also serve as a sensitivity analysis to demonstrate the robustness of PFS based on LE
- **BICR as an audit tool**
  - Complete-case BICR vs. BICR audit
  - BICR conducted in a random sample to detect potential evaluation bias
  - Dodd 2011, Amit 2011, Stone 2015

BICR Audit – Amit 2011

- **Key question**
  - "whether discordance represents systematic bias/unreliability in the estimate of the treatment effect, or whether such discordance is simply a reflection of the variability inherent in the process." – Amit 2011
- **Zhang 2013 (DOI: 10.1158/1078-0432.CCR-12-3364)**

Table 4: Evaluation Results for Method A and Method B

Study	N	Tumor type[1]	LE HR (95% CI)	CC BICR HR (95% CI)	HR Ratio (BICR / LE)	Method A			Method B	
						% CC audits[2]	Mean audit size[2]	% replicate audits confirming LE[3]	% CC audits (0.100)[4]	% CC audits (0.075)[5]
1	752	MBC	0.79 (0.68, 0.91)	0.74 (0.64, 0.87)	0.94	0%	73%	100%	14.8%	23.2%
2	722	MBC	0.49 (0.40, 0.59)	0.54 (0.44, 0.67)	1.10	5%	29%	100%	48.4%	57.7%
3-HER2-	952	MBC	0.89 (0.76, 1.04)	0.96 (0.78, 1.20)	1.08	100%	100%	0	26.1%	37.1%
3-HER2+	219	MBC	0.72 (0.54, 0.97)	0.67 (0.45, 0.99)	0.93	100%	100%	100	21.2%	39.6%
4-Anth	622	MBC	0.66 (0.54, 0.81)	0.79 (0.63, 1.00)	1.20	78%	86%	36%	66.0%	75.3%
4-Cap	615	MBC	0.67 (0.56, 0.82)	0.70 (0.56, 0.87)	1.04	32%	55%	100%	29.6%	38.7%
5	762	MBC	0.81 (0.68, 0.95)	0.86 (0.72, 1.04)	1.06	100%	100%	0%	48.0%	58.0%
6	724	MBC	0.44 (0.36, 0.55)	0.35 (0.27, 0.46)	0.80	0%	30%	100%	4.9%	8.0%
7	769	RCC	0.44 (0.35, 0.54)	0.45 (0.37, 0.56)	1.02	0%	30%	100%	30.8%	38.9%
8	750	RCC	0.41 (0.33, 0.52)	0.41 (0.31, 0.53)	1.00	0%	35%	100%	23.4%	30.2%
9-25mg	416	RCC	0.70 (0.58, 0.86)	0.68 (0.55, 0.85)	0.97	2%	61%	100%	15.6%	25.6%
9-15mg	417	RCC	0.75 (0.61, 0.92)	0.76 (0.62, 0.94)	1.01	100%	100%	100%	3.7%	7.6%
10	416	RCC	0.33 (0.26, 0.42)	0.33 (0.26, 0.43)	1.00	0%	35%	100%	17.4%	24.1%
11	649	RCC	0.62 (0.51, 0.75)	0.59 (0.47, 0.74)	0.95	21%	41%	100%	19.4%	27.3%
12	435	RCC	0.43 (0.34, 0.54)	0.41 (0.32, 0.54)	0.95	0%	35%	100%	19.8%	29.0%
13	723	RCC	0.68 (0.56, 0.82)	0.68 (0.56, 0.83)	1.00	14%	49%	100%	24.5%	33.7%
14	463	MCRC	0.39 (0.32, 0.48)	0.55 (0.45, 0.67)	1.41	5%	29%	100%	98.2%	99.0%
15-Oxal	812	MCRC	1.35 (1.09, 1.67)	1.38 (1.08, 1.77)	1.02	100%	100%	0%	45.5%	54.7%
16-WT	656	MCRC	0.81 (0.67, 0.98)	0.80 (0.66, 0.98)	0.99	100%	100%	100%	25.6%	34.0%
16-Mu	527	MCRC	1.15 (0.95, 1.40)	1.22 (1.00, 1.50)	1.06	100%	100%	0%	16.4%	26.8%
17-WT	597	MCRC	0.71 (0.58, 0.87)	0.75 (0.62, 0.92)	1.06	16%	68%	100%	24.5%	33.4%
17-Mu	589	MCRC	0.82 (0.67, 0.99)	0.90 (0.74, 1.10)	1.10	100%	100%	0%	64.3%	74.6%
18	663	NSCLC	0.50 (0.41, 0.60)	0.63 (0.52, 0.76)	1.26	32%	46%	100%	53.4%	62.2%
19	884	NSCLC	0.71 (0.61, 0.82)	0.71 (0.60, 0.83)	1.00	29%	46%	100%	17.4%	24.8%
20	171	PNET	0.42 (0.26, 0.66)	0.31 (0.18, 0.54)	0.74	1%	55%	100%	0.0%	0.0%
21	410	PNET	0.38 (0.29, 0.48)	0.40 (0.30, 0.54)	1.05	0%	40%	100%	77.4%	84.7%
22	711	STS	0.72 (0.61, 0.85)	0.76 (0.64, 0.90)	1.06	28%	48%	100%	41.4%	51.7%
23	369	STS	0.35 (0.28, 0.45)	0.31 (0.24, 0.41)	0.89	0%	35%	100%	10.4%	16.0%
24	312	GIST	0.29 (0.20, 0.40)	0.32 (0.23, 0.45)	1.10	0%	40%	100%	56.5%	65.5%
25	645	Ovarian	0.69 (0.58, 0.82)	0.79 (0.65, 0.96)	1.14	67%	80%	100%	55.5%	66.0%
26	429	Carcinoid	0.78 (0.62, 0.98)	0.93 (0.71, 1.22)	1.19	100%	100%	0%	22.1%	32.7%

Abbreviations: Anth = anthracycline; Cap = capecitabine; Oxal = oxaliplatin; WT = wild type; Mu = mutant; CC = complete-case; DD = differential discordance

[1]MBC = metastatic breast cancer, RCC = renal cell carcinoma, MCRC = metastatic colorectal cancer, NSCLC = non-small cell lung cancer, PNET = pancreatic neuroendocrine tumors, STS = soft tissue sarcoma, GIST = gastrointestinal stromal tumor; [2]over the 10,000 replicates per study; [3]% of 10,000 audit replicates (whether partial or CC) per study in which consistency of the PFS treatment effect is concluded (i.e. the LE result is confirmed); [4]% of 10,000 replicate audits per study for which CC audit is recommended (i.e. differential discordance (DD) in EDR < -0.100 or DD in LDR > 0.100); [5]% of 10,000 replicate audits for which CC audit is recommended (i.e. DD in EDR < -0.075 or DD in LDR > 0.075)

BICR Audit – Amit 2011 (cont.)

- **Differential discordance**
  - Difference between treatment arms in discordance rates
  - Basic framework for evaluating/detecting bias in LE

Table 1 – BICR versus LE disease progression assessments.

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

Note: In practice a LE PD occurring later than a BICR PD ($a3$) would be observed rarely.
$a1$: number of agreements on timing and occurrence of PD.
$a2$: number of times LE declares PD later than BICR.
$a3$: number of times LE declares PD earlier than BICR.

Amit 2011 (doi:10.1016/j.ejca.2011.02.013)

$$EDR = \frac{b + a3}{a + b}$$

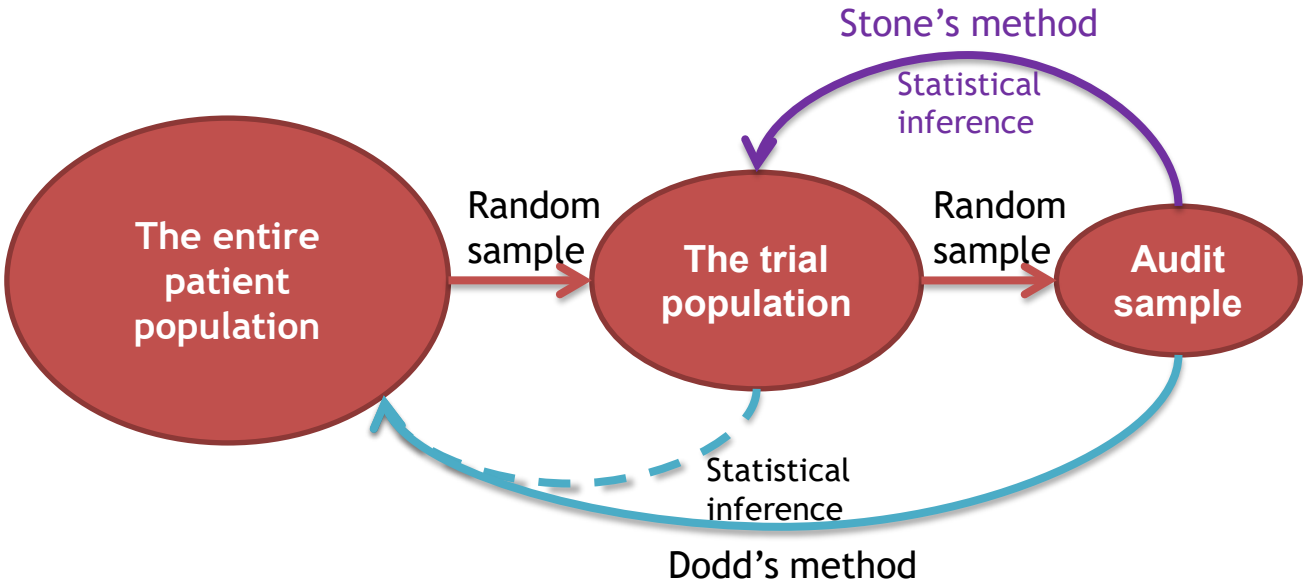
Early Discrepancy Rate (EDR):
LE calling PD earlier than BICR

$$LDR = \frac{c + a2}{b + c + a2 + a3}$$

Late Discrepancy Rate (LDR):
LE calling PD later than BICR

- **Go to full BICR if Δ_{LDR} or Δ_{EDR} > threshold value in BICR audit**

Dodd 2011 and Stone 2015



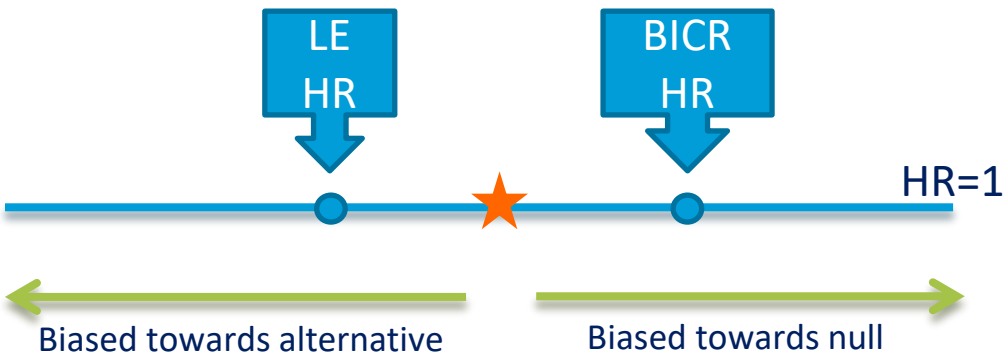
	Dodd 2011	Stone 2015
Underlying Population Parameter	HR_{BICR} in the entire population	HR_{BICR}/HR_{LE} in the trial population (i.e., HRR_F_hat)
Statistical Inference Approach	Estimation (efficient estimator) $\ln(HR_{BICR,S}\_hat)-\lambda\ln(HR_{LE,S}\_hat)+\lambda\ln(HR_{LE,F\text{-}S}\_hat)$	Hypothesis testing H_0: HRR_F_hat ≥ HRR_U
Decision Making	If upper confidence limit < CIF, audit only; otherwise, full BICR	If reject H_0, audit only; otherwise, full BICR

Informative Censoring for estimation bias in PFS

- **Evaluation bias in LE may lead to estimation bias**
  - Evaluation bias may be introduced by the subjective aspect of the disease evaluation in PFS
  - When patients and investigators are unblinded to treatment assignment, PD ma be declared earlier in one arm than the other in a systematic fashion
- **PFS estimated from BICR data may have less evaluation bias**
  - PFS based on BICR can be the primary analysis
  - PFS based on BICR can also serve as a sensitivity analysis to demonstrate the robustness of PFS based on LE
- **PFS estimated from BICR data may have estimation bias resulted from informative censoring (if it occurs more frequently in one arm than the other)**

Informative Censoring (cont.)

- **Example**
  - Retrospective BICR was used
  - Potential evaluation bias: early call of PD in control arm
  - No scans were collected after PD per LE → censoring in BICR for these local PDs



- Retrieve scans after locally determined PD
- Utilize late survival information, e.g., interval-censored methods
- Impute data