Blinded Independent Central Imaging in Clinical Trials: Does it ensure Against Bias?

Sunil Aggarwal[1]*, Raghavendra Rao MV[1], Gaurang Prabhu[1], Sanju Aggarwal[1], David A[1], Jasreen G[1] and Somya A[2]

[1]*Avalon University School of Medicine, Netherlands*
[2]*Rochester Institute of technology, USA*

Submission: March 01, 2016; **Published:** March 05, 2016

***Corresponding author:** Sunil Aggarwal, Avalon University School of Medicine, 122-124 Santa Rosaweg, Willemstad, Netherlands Antilles, Tel: +17176221264; Email: drsunilaggarwal@gmail.com

Abstract

Blinded independent central imaging reads (BICR) are compared against the local evaluation of site. In clinical trials, it has been noted that BICR have lesser bias in comparison to local evaluation. The discordance rates in central reads may still exist but its advantages over weighs the existing dis-advantages. Overall survival measurement still remains the gold standard for any compound efficacy although progression free survival measurement needs to be well documented, if a compound is so tested. There is always a potential for informative censoring with central reads.

Keywords: Blinded independent central imaging, local evaluation, site, bias, discordance, clinical trials, overall survival, progression free survival

Introduction

Blinded independent central reads (BICR) implies the central reads of imaging end -points by one or more radiologists centrally who are blinded for clinical trials and collection of the ultimate data so obtained by medical imaging for regulatory approvals. It has been now well debated if blinded independent central imaging is the best way forward in imaging clinical trials. In this article, we will contrast between central reads and site reads and see if the central reads are best for regulatory approvals in a drug development clinical trial and that if they are free of bias in a clinical trial. "When possible, studies should be blinded. Blinding is particularly important when patient or investigator assessments are included as components of the progression endpoint. At a minimum, the assessments should be subjected to a blinded independent adjudication team, generally consisting of radiologists and clinicians" [1].

Measure of BICR

Overall survival (OS) of a subject in oncology trial has been the benchmark for a favorable outcome of a drug that is being tested. Overall survival is time from randomization until death of the subject in the trials. When there is non-randomization, it is the time from enrollment of a subject in the clinical trial is taken into account. Overall survival gives most accurate assessment of patient benefit [2]. However, overall survival requires larger patient population for evaluation and thus may take longer time. Progression free survival (PFS) has been also widely used to assess the progress of the disease for the subject when inducted in a trial. PFS is already an accepted endpoint in many adjuvant clinical trials [3]. However, PFS may vary in different trials and cannot be classified as a substitute when compared to OS but it may need a smaller trial population, which is an advantage. If we are using PFS as a measure, then it must clearly demonstrate that PFS is indeed present.

BICR Versus Local Evaluation Discordance

Local evaluation is done by the readers who are not centrally located, just like at the site. Most of the time, different radiologists are involved in the reads for various time points, and this causes discordance as mostly the comparison is made with the previous time point and not the baseline. There may not be any measurements of the tumors made by the local radiologists, as well. The training may be

one time and short whereas it is intensive and recurrent with central readers. The reading platforms and monitor displays may vary and do not display special software for the local evaluators, most of the time. Thus, it is clearly evident that there is a bigger potential for bias with local evaluators than the central readers. United States Food and Drug Administration Oncologic Drug Advisory Committee has discussed the discordance issues between local evaluation site reads and independent central imaging [4].

Bias in BICR

Bias in clinical trials is universal although its frequency varies as per the study design [5]. BICR is also not always free of bias. There is a possibility of informative censoring with central reads as subjects may drop out and cause information leak to cause changed outcome of the ultimate outcome of the clinical trial [6]. Treatment effect bias also remains a point of concern with BICR [7-8]. Although in comparison to local reads, central readers have a comparatively less discordance rate, but still it may be high.

Advantages of BICR

BICR certainly displays advantages over local evaluation. One of the most important factor is that central reads decrease systematic imaging reader bias [9]. This helps to produce more consistent reports and better tumor measurements. The overall metrics for the central readers are monitored and better control on the quality of clinical trial reads can be administered as the reads are centrally located and data is reproducible. All this helps to minimize discordance.

Conclusion

BICR remains the most important tool for clinical trials for the regulatory purposes, including a free and fair clinical trial and most widely accepted. Full BICR study should be considered whenever there is a need to increase the confidence in local evaluation [9]. There might be future prospects of local evaluation site assessments with a subset of blinded central reads, but it is the BICR which holds firm ground, at present.

References

1. Johnson JR, Williams G, Pazdur R (2003) Clinical trial endpoints for the approval of cancer drugs and biologics. US Department of Health and Human Services 2007. Rockville, Maryland, USA. J Clin Oncol 21: 1404-1411.

2. Hotte SJ, Bjarnason GA (2011) Progression-free survival as a clinical trial endpoint in advanced renal cell carcinoma. Curr Oncol 18(Suppl 2): S11-S19.

3. Blumenthal GM, Cortazar P, Zhang JJ, Tang S, Sridhara R, et al. (2012) FDA Approval Summary: Sunitinib for the Treatment of Progressive Well-Differentiated Locally Advanced or Metastatic Pancreatic Neuroendocrine Tumors. Oncologist 17(8): 1108-1113.

4. Sica GT (2006) Bias in Research Studies. Radiology 238(3): 780-789.

5. Shih W (2002) Problems in dealing with missing data and informative censoring in clinical trials. Curr Control Trials Cardiovasc Med 3(1): 4.

6. Priya R, Pramesh CS (2012) Censoring in survival analysis: Potential for bias. Perspect Clin Res 3(1): 40.

7. Juni P, Altman DG, Egger M (2001) Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ 323(7303): 42-46.

8. Dodd LE, Korn EL, Freidlin B, Jaffe CC, Rubinstein LV, et al. (2008) Blinded Independent Central Review of Progression-Free Survival in Phase III Clinical Trials: Important Design Element or Unnecessary Expense? J Clin Oncol 26(22): 3791-3796.

9. Amit O, Mannino F, Stone AM, Bushnell W, Denne J, et al. (2011) Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer 47(12): 1772-1778.