

- Implement a requirement that study subjects had already received some sort of therapy for the disease (first line therapy) before enrolling in the clinical study (129,130)
- Increase the maximally allowed time frame between presentation of the disease and enrollment/randomization in the clinical trial (131). The mean time frame for this clinical trial, which involved acute coronary syndrome, was 5.6 hours.

Once the proposed amendment is approved, subsequent versions of the Clinical Study Protocol list the dates of the amendments on the title page of the Clinical Study Protocol (132).

<sup>129</sup> Schiller JH, Larson T, Ou SH, et al. Efficacy and safety of axitinib in patients with advanced non-small-cell lung cancer: results from a phase II study. *J Clin Oncol.* 2009;27:3836–3841.

<sup>130</sup> Blackwell KL, Pegram MD, Tan-Chiu E, et al. Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. *Ann Oncol.* 2009;20:1026–1031.

<sup>131</sup> Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatid in acute coronary syndromes. *New Engl J Med.* 2009;360:2176–2190.

<sup>132</sup> Wood LF, Foote MA. *Targeted Regulatory Writing Techniques.* Clinical Documents for Drugs and Biologics. Basel/Switzerland: Birkhäuser Verlag 2009;pp.55, 73, 77.