Positive Impact of Revised FDA guidance on Clinical Trial Design in Diabetes

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We have investigated the impact of the 2008 revised US Food and Drug Administration (FDA) guidance, requiring robust assessment of cardiovascular safety for all new antidiabetic drugs, on the design and nature of clinical outcome studies.

Clinicaltrials.gov was searched for interventional Phase 2 or higher glucose-lowering drug trials with primary cardiovascular (CV) outcomes and compared trial characteristics of those registered within 3 years before and after the guidance was issued.

For the period March 2008 February 2011 versus March 2005 February 2008, the number of diabetes CV outcomes trials doubled (8 versus 16), and they were larger with median (IQR) 6000 (4082-9313) versus 1116 (300-4447) participants. Later trials had a wider international distribution of participants, with median 27 (6-35) countries recruiting in 501 (183-635) sites versus 17 (1-20) countries recruiting in 160 (3-332) sites. Nine of 16 trials registered after March 2008 recruited worldwide, with all having sites in North and South America, Europe, Australasia and Africa. None of the trials registered in the prior period recruited in all these regions. In the latter period CV composite endpoints contained fewer components, typically CV mortality, nonfatal myocardial infarction, nonfatal stroke, with or without CV hospitalization (13/16 trials), than earlier trials which included additional components, e.g. peripheral artery disease interventions, coronary angioplasty.

Contrary to some expectations, the revised FDA guidance requiring more stringent CV outcomes assessment for diabetes medications did not diminish investment in diabetes outcomes research. The new generation of clinical trials are more globally representative and substantially larger, permitting more definitive estimates of potential benefits and risks that will more definitively inform the future management of diabetes.