Reference safety information guidance

The MHRA Blog "Reference Safety Information (RSI) for Clinical Trials- Part I,II and III" : available on the MHRA website - should be read in conjunction with this guidance.

The Chief Investigator (CI) must ensure that the protocol defines the RSI for the study.

The RSI must be assessed annually as part of the development safety update report (DSUR) submission. If there are any changes to the RSI during the study the CI must assess, with the sponsor, whether or not the protocol and patient facing documents (patient information sheet and consent forms) need to be formally amended.

Once a decision has been made that an update to the RSI document is required, it is important that the change is managed in a timely fashion. The overall process to change the RSI requires several steps, such as a review of the evidence of the proposed change, agreeing the wording, compiling a variation document (where required) awaiting approval by the competent authority (where required), notifying relevant parties of approved updates and implementing changes within an appropriate timeframe. It is not possible to define the timeline for the whole process but the CI should ensure that the updates of the summary of product characteristics (SmPC) and investigators brochure (IB) are performed without undue delay, as they provide vital information to patients and prescribers that will impact upon patient safety.

The IB or SmPC must be reviewed periodically, to ensure that it is up to data and accurately reflects the knowledge currently available about the product. IBs should be reviewed at least annually and revised as necessary. The requirements for reviewing SmPCs is less well defined, although the Directive 2001/83/EC requires that the information should be updated on a 'regular basis,' which the Joint Research Management Office (JRMO) has set the standard as being at least annually.

It is good practice to create a study or unit specific Standard Operating Procedure (SOP) and log for tracking and evidencing the review has occurred

Once approved by the sponsor and competent authority (where required), the CI must ensure that the latest version of the RSI, i.e. the SmPC or IB, is distributed to the PI at each site at the commencement of the trial and when updated. The previous version must be superseded in the TMF and a copy of the updated document placed in the file.

It is vital to have a consistent implementation date for all RSI documents and new version of the RSI, this should be consistent within a study across all sites and countries.