Medicines & Healthcare products Regulatory Agency

Approvals from other authorities
All changes to a non-first-in-human trial have been reviewed and approved as part of a substantial amendment or modification in the EU, EEA, or USA*, provided that the UK modification includes the same version of the documents and does not include any UK-specific aspects
Changes to the protocol
A change to the primary objective of the clinical trial
Use of new measurements for the primary endpoint
Changes to the trial design which have a significant impact on statistical consideration
Changes to how the end of trial is defined (except when this is solely a change to the planned end date)
In trials involving an IMP authorised for use in the UK and used according to that authorisation, a change to the number of planned interactions with the participants to assess their ongoing safety in the trial, unless the change is in response to a new safety concern (which is a Route A substantial modification)
Changes to the list of concomitant medications that the participant can or cannot take
Inclusion of a UK-specific addendum or protocol into a global protocol version, unless the addendum or protocol results in a change to approved safety reporting
Changes to the Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)
Addition of new toxicological or pharmacological data relating to the IMP (including new interpretations of data) of relevance for the investigator, unless changes to the protocol are required from a safety perspective (which is a Route A substantial modification)
Changes to the reference safety information (RSI) involving an increase in frequencies with no new expected adverse reactions

Changes to the IB that do not change the initial risk and benefit assessment of the study or the safety profile of the IMP that was approved by the authorities
Updates to section 4.8 in the SmPC when this is used as the supporting document in place of an IB for an IMP (i.e. when section 4.8 is considered the RSI)

***** As evidence that changes have been reviewed and approved by the USA, the sponsor should provide confirmation that the investigational new drug (IND) application amendment has been submitted to the FDA, including the applicable reference or tracking number. In addition, confirmation should be provided that the required waiting period following submission of the IND amendment has elapsed and that no objections were issued by the FDA during this period.