# Clinical Trials Notification Scheme FAQs

Q: The risk associated with the IMP in a proposed clinical trial is considered to be no higher than that of standard medical care. As such, the Sponsor considers the trial to fall into the category of Type A. Can this trial be submitted under the Notification Scheme?

A: Clinical Trial Notifications can only be made for Type A trials involving medicinal products licensed in any EU Member State if they relate to the licensed range of indications, dosage and form or, they involve off-label use if this off-label use is established practice and supported by sufficient published evidence and/or guidelines. Type B and Type C trials are not eligible for submission under the Notification Scheme.

Type B and C trials are those in which the potential risk associated with the IMP is somewhat higher or markedly higher than that of standard medical care, respectively. Clinical Trial Authorisation applications for trials in these two categories require a full assessment and are not eligible for the Notification Scheme.

Q: Why are placebo controlled clinical trials not eligible for submission under the Notification Scheme?

A: One of the eligibility criteria for submission under the Notification Scheme is that the risk to trial participants is considered to be no higher than that of standard medical care. Trial subjects receiving placebo are being denied the potential benefits of standard therapy and, therefore, the risk to them would be considered higher than that of standard medical care.

Q: There is no established standard medical care for the indication under investigation. Under these circumstances would it be acceptable to include a placebo control arm in a trial submitted under the Notification Scheme?

A: In these circumstances it may be acceptable to include a placebo control arm. However, robust evidence would need to be provided in order to demonstrate the absence of any standard therapy for the condition under investigation.

The applicant is also reminded that the use of any unlicensed medicinal product in the trial renders the study ineligible for submission under the Notification Scheme. Therefore, any placebo comparator product would also have to be licensed in an EU Member State.

Trials involving unlicensed placebo comparators are not eligible for the Notification Scheme due to the additional risk to trial subjects associated with the administration of an unlicensed medicinal product and due to the additional assessment of the CTA application required by the MHRA. The MHRA agreed a 14 day period, in which the submission could be reviewed and, if necessary, an objection to the notification raised, on the basis that a Quality assessment of the IMPs would not be required.

Q: If a trial has a placebo arm is it automatically Type C?

A: No, it could be A, B, or C. Trial subjects receiving placebo are potentially being denied the benefits of standard therapy and, therefore, the risk to them (from the disease itself rather than treatment) may be considered higher than that of standard medical care. In addition placebos are normally unlicensed and therefore will carry an additional risk associated with the administration of an unlicensed product. Hence, the trial would be Type B or C depending on the disease characteristics, patient factors as well as the risks associated with the active comparator. In circumstances where there is no established standard of care for the indication under investigation, it may be acceptable to categorise the placebo-controlled trial as Type A, if the placebo used is licensed. However, robust evidence would need to be provided in order to demonstrate the absence of any standard therapy for the condition under investigation.

Q: Are trials in which blinding is achieved through the use of a double dummy design eligible for submission under the Notification Scheme, as all participants will receive the test IMP or standard medical care plus placebo?

A: Yes, trials in which blinding is achieved through the use of a double dummy design are eligible for the Notification Scheme providing all IMPs, including placebo, are licensed in an EU Member State.

Q: An EU-licensed product will be over-encapsulated for blinding purposes. Can the trial be submitted under the Notification Scheme?

A: No, the trial would not be eligible for the Notification Scheme. This is due to the additional potential risk to trial subjects associated with the administration of a modified licensed product and the additional assessment of the CTA application required by the MHRA. The MHRA agreed a 14 day period, in which the submission could be reviewed and, if necessary, an objection to the notification raised, on the basis that a Quality assessment of the IMPs would not be required.

Q: An EU-licensed product will be repackaged and relabelled for blinding purposes. Can the trial be submitted under the Notification Scheme?

A: Yes, repackaging and/or relabeling of an EU-licensed product does not affect the trial's eligibility for submission under the Notification Scheme.

Q: A drug product, licensed for many years for the treatment of adult patients, has been reformulated for use in a paediatric population. The reformulated product is currently unlicensed. Can a trial involving this paediatric formulation be submitted under the Notification Scheme?

A: No, the trial would not be eligible for the Notification Scheme. This is due to the additional potential risk to trial subjects associated with the administration of an unlicensed product and the additional assessment of the CTA application required by

the MHRA. The MHRA agreed a 14 day period, in which the submission could be reviewed and, if necessary, an objection to the notification raised, on the basis that a Quality assessment of the IMPs would not be required.

Q: An unmodified, EU-licensed product is intended for use in a clinical trial but outside of its licensed indications. The trial is considered to be a Type A trial as use of the IMP for treatment of this condition is established medical practice. What evidence is required to demonstrate that the proposed therapy is standard medical care?

A: The Notification should include a rationale/justification for use of the licensed product, outside the terms of its SmPC, in the proposed trial. This should be supported by published evidence and/or guidelines establishing the therapy as accepted medical practice, for example NICE guidelines or peer-reviewed publications. Where publications are provided as supporting documentation, a summary should also be included.

Q: If risk increases from Type A to Type B does the MHRA need to re-review the protocol?

A: Yes, this will mean the risk: benefit analysis for the trial participants has been changed and will need to be submitted as a substantial amendment. However, if the modifications to the use of IMP in the trial are still within the terms of SmPC (with regards to the indication, subject population, dosage, etc) then it is unlikely to affect the risk category of the trial and the MHRA does not need to be notified.

Q: What circumstances would be required for a trial of an unlicensed IMP to be downgraded in risk to Type B?

A: This will only be applicable in a minority of cases. For example, a clinical trial involving the use of an unlicensed paediatric reformulation of a licensed product that has been used in the adult population for several years may be classed as a type B trial.
For most unlicensed products, the downgrading of risk category from C to B largely depends on the clinical experience with the IMP at the time of application for a CTA. It is expected that the IMP would have at least entered Phase III of its development and preferably, pivotal study would have been completed. Further, safety signals from pre-clinical studies, safety and tolerability data from previous clinical experience, the extent of required safety monitoring and the type of patient population to be treated will all need to be taken into account in assessing the risk category.

Q: Will use of the IMP, rather than nature of the IMP (Risk A) be included in Risk “B” list? Misuse of IMP is a severe risk only slightly related to nature of IMP but greatly related to clinical trial process.

A: Yes, for example, if the use of IMP outside its licensed indications and/or substantial dosage modifications is made from the licensed dosage, then the trial may belong to Type B category.

Q: Can a guidance algorithm be devised?

A: We do not believe that an algorithm will offer any significant advantage to sponsors in utilising risk-adapted approaches to their clinical trials.