GUIDELINES FOR CO-ENROLMENT

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1 INTRODUCTION

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 There are no direct statements regarding co-enrolment in the Medicines for Human Use (Clinical Trials) Act SI 2004/1031 (as amended) - transposed from EU Directive 2001/20/EC.

1.3 The Journal of the Intensive Care Society released an editorial (volume 4, number 2, April 2013) concerning co-enrolment. It described a number of issues that should be considered before co-enrolment is sanctioned. These issues included: study design and statistical considerations; legal and ethical considerations; biological and scientific rationale; participant considerations and; logistical and organisational issues.

1.4 The Association of the British Pharmaceutical Industry (ABPI) guidelines state that there should be a 4-month period between participation in Clinical Trials of Investigational Medicinal Products (CTIMPs). This would preclude participation in two CTIMPs simultaneously.

1.5 A meeting of the National Research Ethics Advisors' Panel (10/July/2013) discussed co-enrolment and provided comment as follows:

- "Researchers should not place blanket restrictions on patients' freedom of action without justifiable reasons for doing so agreed with the REC."
- "RECs should look closely at any project that stipulates that participants should not take part in any other studies to assure themselves that any such restriction was necessary, primarily for participants' safety. This applies especially to studies involving long-term follow-up of participants."
- The panel do not agree with the ABPI position with regards to a four-month washout period between participation in CTIMPs and preferred that the washout period might vary depending on the trials involved but should always be clinically informed and justified."

2 SCOPE

2.1 This document is relevant to all researchers participating in or organising research studies sponsored by NHSL and/or the UoE.

2.2 This document is relevant to all members of ACCORD who facilitate, manage, co-ordinate or advise on clinical research sponsored by NHSL and/or the UoE.

2.3 This document is relevant to research where individual participant consent is taken.

3 GUIDELINES

3.1 Communication of Co-Enrolment Plans

3.1.1 Co-enrolment will be considered and may be permitted in studies sponsored by NHSL and/or the UoE, in compliance with the study protocol.

3.1.2 The Sponsor's representatives require details of the proposed co-enrolment to be described to the Sponsor(s), the Research Ethics Committee (REC) and the Competent Authority (CA) where applicable.

3.1.3 The Sponsor's representatives also require Investigators from all studies involved in co-enrolment to be aware of the co-enrolment plans and provide documented permission for co-enrolment to be undertaken in their study.

3.1.4 Details of co-enrolment may entail identifying specific studies with which co-enrolment will be permitted. Alternatively, there may be situations where generic circumstances can be described, defining when co-enrolment can be permitted. For example, co-enrolment could be permitted with studies that involve only the collection of data (e.g. questionnaires) or tissue samples (e.g. blood). If patient follow-up is required, consideration may need to be given as to whether the follow up outcome measures could be influenced by participation in other co-enrolling studies especially where they involve a trial intervention.

3.2 Considerations for Co-Enrolment Plans

3.2.1 Phase I Trials
Co-enrolment will not be permitted for Interventional or experimental studies where one or more of the studies concerned are classified as First-Time-Into-Human studies or a CTIMP Phase I study.

3.2.2 Interventional Trials
It is recommended that a washout period should be defined if there is an intention to allow co-enrolment between studies involving interventions. For CTIMPs, Sponsor's representatives and Investigators should consider

seeking the opinion of a clinical pharmacologist, who can be considered independent of both studies, regarding the length of a minimum wash-out period. Pharmacokinetic (absorption, distribution, metabolism and excretion) and pharmacodynamics (drug action including binding and interactions) effects should be considered in such an assessment. Similar considerations should be made for other non-CTIMP pharmaceutical interventions as well as other non-pharmaceutical interventions such as diagnostic, radiation, device or surgical interventions.

3.2.3 Participant Burden

It is recommended that overall burden to participants should be given due consideration by Investigators and Sponsors. Consideration of burden should include follow-up requirements including participant based follow-up such as self-completing questionnaires. For example, participants completing questionnaires for multiple studies in the same or similar disease groups may present a risk of participant non-compliance due to burden and/or confusion over which questionnaires to complete.

3.2.4 Study Design and Outcomes

It is recommended that consideration be given to whether co-enrolment is likely to influence the outcome measures and end-points of the trials, or compromise the overall study design and delivery. Even for non-interventional observational studies where the outcomes may be questionnaire data, it is possible responses provided for one study may alter responses given in another study.

It is also recommended that co-enrolment proposals be provided to statisticians representing each study, where a statistician has been identified, to determine if study outcomes could be affected.

Furthermore, it is recommended that co-enrolment proposals be provided to the Trial Steering Committee (TSC) and/or Data Management Committee (DMC) for each study, if one has been assembled or is intended to be assembled, The TSC/DMC should consider any potential for co-enrolment to: compromise study design; affect study outcomes for example by introducing bias; adversely affect participant safety and; increase participant burden such that risk outweighs benefit. The TSC/DMC should also consider the compatibility of both protocols for example, ensure that eligibility criteria and prohibited concomitant medications cannot compromise co-enrolment plans and ensure that co-enrolment plans do not alter any expected/required enrolment distribution models.

3.3 Safeguards

3.3.1 CTIMP-CTIMP Agreement

The Sponsor's representatives require proposals for co-enrolment between CTIMP studies to be captured in a written, authorised agreement between the Sponsors and Investigators of each study. The agreement should include:

- the agreed washout period;
- a description of the circumstances in which co-enrolment will take place (e.g. which study will participants first be enrolled into, any co-enrolment eligibility rules);
- a statement of the potential effect of co-enrolment on study outcomes;
- a statement from the Sponsors and Investigators that the anticipated overall burden to participants is reasonable to bear and the risk-benefit balance will not be altered;
- a statement from the chairs of the TSC/DMC from each study that they have no objections to the proposals for co-enrolment and;
- a statement that arrangements for attribution of liability for co-enrolled participants have been put in place.

3.3.2 Accidental/Unintentional Co-Enrolment

It is recommended that systems are implemented by Investigators to prevent accidental/unintentional co-enrolment. Systems may include keeping a study record of all participants who have been co-enrolled and utilising shared patient information databases (e.g. TrakCare) to check on the enrolment status of a participant. Furthermore, it is recommended that Investigators routinely ask participants if they are enrolled in another study.

The Sponsor's representatives require that incidents of accidental/unintentional co-enrolment by reported to the Sponsor as a protocol deviation/violation, in accordance with SOP CR010.

4 REFERENCES AND RELATED DOCUMENTS

- The Medicines for Human Use (Clinical Trials) Regulations (SI 2004 No. 1031), as amended.
- Editorial: the Journal of the Intensive Care Society, volume 4, number 2, April 2013.
- National Research Ethics Advisors' Panel meeting, 10/July/2013
- Association of the British Pharmaceutical Industry (ABPI) guidelines
- SOP CR010 Management of Protocol Deviations and Violations

5 DOCUMENT HISTORY

Version Number	Effective Date	Reason for Change
1.0	29 APR 2014	First version of new document
2.0	18 MAY 2016	New guideline template and title. Exemption of co-enrolment for all first in human/Phase I studies removed from section 3.1. Considerations for Co-Enrolment Plans – Phase I Trials added (section 3.2.1).

6 APPROVALS

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