Combined Ways of Working Pilot – Application Dossier Guidance

(version 3.4)

Introduction and scope of document

The purpose of this document is to provide best practice guidance for the submission of an application into the Combined Ways of Working Pilot. This is guidance only and does not contain criteria which are required for an application dossier to be considered valid.

Applications for a Clinical Trial Authorisation and to a Research Ethics Committee into the Combined ways of Working Pilot must comply with CT-1 (Detailed guidance on the request to the competent authorities for authorisation of a clinical trial of a medicinal product for human use, the notification of substantial amendments and the declaration of the end of trial) and CT-2 (Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use).This guidance document follows the structure of the EU Clinical Trial Regulation (536/2014), this is because we want to ensure that the Combined Ways of Working process which we are developing will also be compliant with any future Regulatory position. However, following this guidance will also ensure that applications will meet the requirements of CT-1 and CT-2.

1. COVER LETTER

The cover letter is used by the Research Ethics Committee (REC) to help the committee members understand why the trial is being undertaken and what it will involve. A clear and comprehensive cover letter really helps the REC review process so it is recommended that the information is written in language which is understandable to a lay person and provides a clear summary of the trial.

The cover letter should always include the following:

- A statement to confirm that the named Sponsor and named Chief Investigator authorise the application.
- A summary of the clinical trial written in language which is understandable to a lay person.
- A description of how the public or relevant patient groups have been involved in the development of the trial, including the development of participant facing documents.
- Checklist of all documents submitted, including dates and version numbers (please note that not all documents in the table below may be appropriate for all trials. Where a document which is listed below is not submitted because it is not relevant or because the information is contained elsewhere in the application dossier, such as in the protocol, then you just need to detail this in the comments column for the purposes of validation)

Information	**Version (if applicable**	**Present (Y/N/NA)**	**Comment**
COVER LETTER			
EudraCT form (IRAS generated) : PDF and XML file			
PROTOCOL			
INVESTIGATOR'S BROCHURE (IB)			
DOCUMENTATION RELATING TO COMPLIANCE WITH GMP			

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)			
AUXILIARY (ie non-IMP) MEDICINAL PRODUCT DOSSIER			
SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP) (If applicable)			
CONTENT OF THE LABELLING OF THE IMP			
RECRUITMENT ARRANGEMENTS			
SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE			
Ethical Considerations Form			
Study Wide Review (NHS only)			
SUITABILITY OF THE INVESTIGATOR (non-NHS only)			
SUITABILITY OF THE FACILITIES (non-NHS only)			
PROOF OF INSURANCE COVER OR INDEMNIFICATION			
FINANCIAL AND OTHER ARRANGEMENTS			
PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION			

- All reference numbers (EudraCT / REC / IRAS)
- Invariable study protocol number (if available)
- Title of the trial.

The cover letter shall state:

- Whether the clinical trial is considered by the sponsor to be a Type A clinical trial suitable for the MHRA notification scheme and shall contain a detailed justification thereof.
- The location in the application dossier of the reference safety information (RSI) necessary for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction

The cover letter should either include a description of or reference the location in the application dossier for the following, where they are relevant to the clinical trial:

- Specific features of the clinical trial population (e.g adults unable to consent, children or pregnant or breastfeeding women).
- Whether the clinical trial involves the first administration of a new active substance to humans
- Whether scientific advice relating to the clinical trial or the investigational medicinal product has been given by the European Medicines Agency (EMA), a Member State or a third country;

- Whether the clinical trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3, of Regulation (EC) No 1901/2006 (if the EMA has already issued a decision on the PIP, the cover letter contains the link to the decision of the EMA on its website)
- Whether investigational medicinal products or non-investigational medicinal products medicinal products are a narcotic, psychotropic or radiopharmaceutical;
- Whether the investigational medicinal products consist of or contain a genetically-modified organism or organisms (ATMP trials are excluded from the initial stage of the pilot)
- Whether the sponsor has obtained an orphan designation for the investigational medicinal product for an orphan condition
- A comprehensive list, including the regulatory status (licensed / un-licensed), of all active investigational medicinal products and a list of all non-investigational medicinal products
- A list of medical devices which are to be investigated in the clinical trial but which are not part of the investigational medicinal product or products, together with a statement as to whether the medical devices are CE-marked for the intended use.

In the case of a resubmission, the cover letter shall include the following:

- The reference numbers of the previous submission (EudraCT / REC / IRAS)
- A summary of the changes made compared to the previous submission
- How any unresolved issues from the previous submission have been addressed (if applicable)

2. EudraCT form (XML & PDF)

- These are generated via IRAS but should be submitted with the application dossier.
- Currently the full IRAS form must be completed and submitted but this document is not provided to the Research Ethics Committee (REC). The REC will only receive the EudraCT form. It is therefore important that issues which are relevant to the REC are clearly and comprehensively explained in the protocol. Additional documents may be provided to describe the recruitment and informed consent procedures if required.

3. Protocol

The protocol is used by the REC when undertaking an ethical review of the proposed trial. Accepting that this document has a broader purpose in the management of a clinical trial, applicants are encouraged to use language which is understandable to a lay person where possible. A clear and understandable protocol will help the REC understand the details of the trial and the expectation is that this will result in fewer request for clarification or further information and may therefore result in a quicker review and approval process.

The protocol shall:

- Describe the objective, design, methodology, statistical considerations, purpose and organisation of the clinical trial in a way which is understandable to a lay person.
- Be identified by: (a) the title of the clinical trial; (b) the EudraCT trial number; (c) the sponsor's protocol code number specific for all versions of it (if relevant); (d) the date and number of the version, to be updated when it is amended; (e) a short title or name assigned to the protocol; and (f) the name and address of the sponsor, as well as the name and function of the representative or representatives of the sponsor authorised to sign the protocol or any substantial modification to the protocol.
- Be written in an easily accessible and searchable format, rather than scanned images (where possible)

Include:

a) A summary of the trial which is understandable to a lay person.
b) A clear and unambiguous definition of the end of the trial in question. In most cases this will be the date of the last visit of the last patient undergoing the trial. Any exceptions should be justified.
c) A description of the plan for the provision of any additional care for the trial participants once their participation in the trial has ended. Where it differs from what is normally expected according to the medical condition of the clinical trial participant.
d) Information to address sub-studies conducted at all trial sites or only at specific sites (if applicable).
e) The relevance of the clinical trial.
f) A statement that the clinical trial is to be conducted in compliance with the protocol, with the relevant Regulations and with the principles of good clinical practice
g) A comprehensive list of all investigational medicinal products and of all non-investigational medicinal products
h) A summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial
i) A summary of the known and potential risks and benefits including an evaluation of the anticipated benefits and risks to allow assessment; for subjects in a clinical trial in an emergency situation, the scientific grounds for expecting that the participation of the subjects has the potential to produce a direct clinically relevant benefit shall be documented
   In order to protect the safety of trial participants, all potential risks associated with the use of all the IMPs have to be addressed in the protocol and risk mitigation strategies have to be proposed.
j) Where patients were involved in the design of the clinical trial, a description of their involvement
k) A description of, and justification for, the dosage, the dosage regime, the route and mode of administration, and the treatment period for all investigational medicinal products and auxiliary medicinal products
l) A statement of whether the investigational medicinal products and non-investigational medicinal products used in the clinical trial are authorised; if authorised, whether they are to be used in the clinical trial in accordance with the terms of their marketing authorisations, and, if not authorised, a justification for the use of non-authorised auxiliary medicinal products in the clinical trial
m) A description of the groups and subgroups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs, for example. age, gender, participation of healthy volunteers, subjects with rare and ultra rare diseases
n) The acceptable methods of contraception, the duration of use (during study and/or after study drug administration), and the frequency of

pregnancy testing. The measures mandated by the protocol must comply with the IB recommendations or the SmPC requirements.
Recommendations related to contraception and pregnancy testing in clinical trials have been developed by the Clinical Trial Facilitation Group.

The study protocol should also contain detailed information on the possibility for an interaction between the IMPs or the non-IMPs and hormonal contraceptives. A pregnancy testing 'no sooner than 7 days before the study drug administration' is recommended or a rationale has to be provided why this is not appropriate.

o) The eligibility criteria; which must be compliant with the IBs and/or SmPCs of IMPs with marketing authorisation, particularly with respect to contraindications and contraceptive requirements
p) A description of the accountability procedures for the supply and administration of medicinal products to subjects including the maintenance of blinding, if applicable
q) If and when knowledge of the treatment assignment is considered necessary to determine the optimal medical management; the treating physician has to have immediate and direct access to the unblinding procedure. clearly stating the trial specific procedure for unblinding in case of medical emergency.
r) References to literature and data that are relevant to the clinical trial, and that provide background for the clinical trial
s) Arrangements for the maintenance of clinical trial treatment randomisation codes and procedures for breaking codes; if relevant.
t) A description of the type of clinical trial to be conducted and a discussion of the trial design (including a schematic diagram of trial design, procedures and stages, if relevant);
u) A specification of the primary end-points and the secondary end-points, if any, to be measured during the clinical trial in accordance with Commission Directive 2005/28/EC, clinical trials should be scientifically sound and guided by ethical principles in all their aspects. Study endpoints form part of the basis of the trial design and this in turn is critical for the scientific integrity of the trial and also the credibility of the data formed. If the aim of the study is to assess efficacy and long term safety, the trial endpoint should reflect this with clinical endpoint(s)
v) A description of the measures taken to minimise bias, including, if applicable, randomisation and blinding
w) A description of the expected duration of subject participation and a description of the sequence and duration of all clinical trial periods, including follow-up, if relevant

x) A description of the criteria for discontinuing parts of the clinical trial or the entire clinical trial
y) A description of procedures for the identification of data to be recorded directly on the Case Report Forms considered as source data
z) A description of the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects, where applicable, unless contained in a separate document
aa) A description of the arrangements for tracing, storing, destroying and returning the investigational medicinal product and unauthorised non-investigational medicinal product
bb) A description of the statistical methods to be employed, including, if relevant:
    - timing of any planned interim analysis and the number of subjects planned to be enrolled;
    - reasons for choice of sample size (stating UK sample size);
    - calculations of the power of the clinical trial and clinical relevance;
    - the level of significance to be used;
    - criteria for the termination of the clinical trial;
    - procedures for accounting for missing, unused, and spurious data and for reporting any deviation from the original statistical plan;
    - the selection of subjects to be included in the analyses;
cc) A description of the subject inclusion and exclusion criteria, including criteria for withdrawing individual subjects from treatment or from the clinical trial
dd) A description of procedures relating to the withdrawal of subjects from treatment or from the clinical trial including procedures for the collection of data regarding withdrawn subjects, procedures for replacement of subjects and the follow-up of subjects that have withdrawn from treatment or from the clinical trial
ee) A justification for including subjects who are incapable of giving informed consent or other special populations, such as minors
ff) A justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria
gg) A detailed description of the recruitment and informed consent procedure, especially when subjects are incapable of giving informed consent
hh) A description of the treatments, including medicinal products, which are permitted or not permitted, before or during the clinical trial
ii) A description of procedures for monitoring subject compliance, if applicable;

jj) A description of arrangements for monitoring the conduct of the clinical trial;

kk) A description of the arrangements for taking care of the subjects after their participation in the clinical trial has ended, where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally expected for the medical condition in question;

ll) A specification of the efficacy and safety parameters as well as the methods and timing for assessing, recording, and analysing these parameters;

mm) A description of ethical considerations relating to the clinical trial if those have not been described elsewhere;

nn) A statement from the sponsor (either in the protocol or in a separate document) confirming that the investigators and institutions involved in the clinical trial are to permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents;

oo) A description of the publication policy;

pp) Duly substantiated reasons for the submission of the summary of the results of the clinical trials after more than one year;

qq) A description of the arrangements to comply with the applicable rules on the protection of personal data; in particular organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed;

rr) A description of measures that will be implemented to ensure confidentiality of records and personal data of subjects;

ss) A description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects.

- If a clinical trial is conducted with an active substance available in the Union under different trade names in a number of authorised medicinal products, the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.
- With regard to the notification of adverse events, the protocol shall identify the categories of: (a) adverse events or laboratory anomalies that are critical to safety evaluations and must be reported by the investigator to the sponsor, and (b) serious adverse events which do not require immediate reporting by the investigator to the sponsor.
- The protocol shall describe the procedures for: (a) eliciting and recording adverse events by the investigator, and the reporting of relevant adverse events by the investigator to the sponsor; (b) reporting by the investigator to

the sponsor of those serious adverse events which have been identified in the protocol as not requiring immediate reporting; (c) reporting of suspected unexpected serious adverse reactions by the sponsor to the Eudravigilance database; and (d) follow-up of subjects after adverse reactions including the type and duration of follow-up.

- In case the sponsor intends to submit a single safety report on all investigational medicinal products used in the clinical trial, the protocol shall indicate the reasons thereof.
- Issues regarding labelling shall be addressed in the protocol, where necessary.
- The protocol shall be accompanied by the Charter of the Data Safety Monitoring Committee, if applicable.
- The protocol shall be accompanied by a synopsis of the protocol which is written in language understandable to a lay person.
- The protocol should be signed by the Sponsor.

4. Investigators Brochure

An investigator's brochure shall:

- Be prepared in accordance with the state of scientific knowledge and international guidance.
- Provide the investigators and others involved in the clinical trial with information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.
- Be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. It shall be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the clinical trial and be presented in the form of summaries.
- Be submitted as the approved summary of product characteristics (SmPC) if the investigational medicinal product is authorised, and is used in accordance with the terms of the marketing authorisation, If the conditions of use in the clinical trial differ from those authorised, the SmPC shall be supplemented with a summary of relevant non-clinical and clinical data that support the use of the investigational medicinal product in the clinical trial. Where the investigational medicinal product is identified in the protocol only by its active substance, the sponsor shall select one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site
- For a multinational clinical trial where the medicinal product to be used in each Member State concerned is authorised at national level, and the SmPC varies among Member States concerned, an SmPC is to be chosen by the sponsor as

the SmPC for the whole clinical trial. This SmPC shall be the one best suited to ensure patient safety.

- If the IB is not an SmPC, contain a clearly identifiable section called the 'Reference Safety Information' (RSI). In accordance with the relevant CTFG guidance http://www.hma.eu/ctfg.html the RSI shall contain product information on the investigational medicinal product and on how to determine what serious adverse reactions are to be considered as expected serious adverse reactions, and on the frequency and nature of those serious adverse reactions.

5. Documentation Relating to Compliance with Good Manufacturing Practice (GMP) for the Investigational Medicinal Product

For documentation relating to GMP compliance, the following should apply (as per Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)):

6. Investigational Medicinal Product Dossier (IMPD)

- The IMPD should be a single document rather than multiple documents. It would be acceptable to split S, P and placebo (if for example one S section relates to multiple product presentations) but, in general, documentation should be as consolidated as possible and in a summarised format.
- All information referred to in the IMPD, e.g. TSE certification, should be included in the IMPD document in the relevant section. There is no need to provide Certificates of Analysis for drug substance or drug product batches; tabulated summaries of batch analysis data in the relevant sections of the IMPD are sufficient.
- The IMPD should be compliant with the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)
- Please note that literature references are not required for quality data and should not be submitted: all data supplied should be trial-specific and included in the IMPD.

7. Auxiliary Medicinal Product Dossier (ie Non-Investigational Medicinal Product Dossier)

- The Non-Investigational Medicinal Product (NIMP) Dossier should follow the Guidance on Investigational Medicinal Products (IMPs) and "non investigational medicinal products" (NIMPs).
- Where the auxiliary medicine is authorised in the UK, no further information is required

8. Scientific Advice and Paediatric Investigation Plan (PIP)

- If available, a copy of the summary of scientific advice of the EMA, or of any Member State or third country, with regard to the clinical trial shall be submitted.
- If the clinical trial is part of an agreed PIP, a copy of the Agency's decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet shall be submitted. In the latter case, a link to this documentation in the cover letter is sufficient.

9. Content of the Labelling of the Investigational Medicinal Products

- A description of the content of the labelling of the investigational medicinal product in accordance with Annex 13 of Volume 4 of the EU Guidelines to Good Manufacturing Practice shall be provided.

10. Recruitment Arrangements

- It is expected that arrangements for recruitment are clearly described in the protocol. This should include how potential participants will be identified.
- Alternatively, if a clear description has not been provided in the protocol, a separate document should be submitted which shall describe in detail the procedures for inclusion of subjects and shall provide a clear indication of what the first act of recruitment is. The following template should be completed (the submission of EU harmonised templates is also acceptable)
- Where the recruitment of subjects is done through advertisement, copies of the advertising material shall be submitted, including any printed materials, and audio or visual recordings. Generic advertisements which have been reviewed and approved by the generic document committee, do not need to be re-submitted. The generically approved advertisements should be referenced in the IRAS checklist and covering letter, the generic reference assigned should be included.
- The procedures proposed for handling responses to the advertisement shall be outlined. This includes copies of communications used to invite subjects to participate in the clinical trial and arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial.

11. Subject Information, Informed Consent Form and Informed Consent Procedure

- The procedure for obtaining informed consent should be described in the protocol or submitted as a separate document. Where submitted in a separate document, the following template should be used (the submission of EU harmonised templates is also acceptable)
- The information provided (whether described in the protocol or a separate document) should contain, as a minimum, a description of procedures relating to informed consent for all subjects, and in particular:

(a) in clinical trials with minors or incapacitated subjects, the procedures to obtain informed consent from the legally designated representatives, and the involvement of the minor or incapacitated subject.
(b) If a procedure with consent witnessed by an impartial witness is to be used, relevant information on the reason for using an impartial witness, on the selection of the impartial witness and on the procedure for obtaining informed consent shall be provided
(c) In the case of clinical trials in emergency situations, the procedure for obtaining the informed consent of the subject or the legally designated representative to continue the clinical trial shall be described
(d) In the case of clinical trials in emergency situations, the description of the procedures followed to identify the urgency of the situation and to document it
(e) In the case of clinical trials where their methodology requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products, and where, as a consequence, simplified means for obtaining informed consent will be used, the simplified means shall be described.

- All information given to the subjects (or, where applicable, to their legally designated representatives) before their decision to participate or abstain from participation shall be submitted together with the form for written informed consent.
- In the cases set out above, the information given to the subject and to his or her legally designated representative shall be submitted.

12. Ethical Considerations Form

- This form should be completed for all applications.

13. Study Wide Review Form

- This form should be completed for all applications for trials taking place in the NHS/HSC.

14. Payment of Compensation

- This form should be completed for all applications.

15. Ionising Radiation form (Part B Section 3 of IRAS)

- Until further notice, the ionising radiation form, as well as authorisation by the Clinical Radiation Expert (CRE) and the Medical Physics Expert (MPE), should be completed in IRAS.
- For trials which involve the administration of radioactive substances, the ARSAC form should also be completed in IRAS.
- PDF versions of the form should be uploaded as a supporting document

16. Suitability of the Investigators

- As a general principle, a list of the planned clinical trial sites, the name and position of the principal investigators and the planned number of subjects at the sites shall be submitted. Currently this is provided via the EudraCT form.
- For trials not taking place in the NHS/HSC, a description of the qualification of the Principal Investigator(s) in a current curriculum vitae (preferably of no more than two pages in length) shall be submitted. Any previous training in the principles of good clinical practice or experience obtained from work with clinical trials and patient care should be described in the CV.
- For trials taking place in the NHS/HSC, the same arrangements as other CTIMPs apply (there is no requirement to provide CVs for Principle Investigators).
- For trials not taking place in the NHS/HSC, any conditions, such as economic interests and institutional affiliations, that might influence the impartiality of the investigators, shall be presented (A template document is available (the submission of EU harmonised templates is also acceptable)).

17. Suitability of the Facilities

- For clinical trials taking place in the NHS, no information about sites is required which is additional to the information which is provided in the EudraCT form.
- For non NHS/HSC sites, either of the following forms are accepted;
    - the non NHS/HSC site form which is available on the HRA website (the submission of EU harmonised templates is also acceptable).

18. Proof of Insurance Cover or Indemnification

- Proof of insurance, a guarantee, or a similar arrangement shall be submitted, if applicable.

19. Financial and Other Arrangements

- Where possible an Industry Costing Template (validated by the lead CRN if the study is on the NIHR portfolio) should be submitted to provide a description of the financing of the trial. From 1 April 2020, the e-mail confirming submission to the NIHR CRN via the iCT in CPMS should be submitted.
- Where this is not available, a brief description of the financing of the clinical trial should be submitted.
- Where possible, the clinical trial agreement(s) (or any other agreement(s)) which the sponsor is going to propose to the site, or the Industry Costing Template should be submitted.
- If not included in the documents above or if the above documents cannot be submitted, information on financial transactions and compensation paid to subjects and investigator/site for participating in the clinical trial shall be submitted.
- Description of any other agreement between the sponsor and the site shall be submitted. Where the sponsor has appointed a legal representative, evidence

has been provided (in the form of a letter from the legal representative or contract with the sponsor) confirming that the legal representative has agreed to undertake this role. The legal representative may be a person or an organisation. No legal qualifications are required.

- Confirmation that the sponsor or the sponsor's legal representative are based in the EEA.

20. Proof That Data Will Be Processed in Compliance with UK Law on Data

- A statement by the sponsor or his or her representative that data will be collected and processed in accordance with existing data protection legislation shall be provided.
- This may be provided in the c over letter, in the protocol or may be a separate document.
- The protocol should also clearly describe how data will be processed in compliance with UK law on data, including whether identification of participants will require access to confidential information.

Summary of document changes

Section	Change	Version	Date
12. Ethical considerations form 13. Study wide review form 14. Payment of compensation form 15. Ionising Radiation	New sections included in the guidance	3.4	2.3.20
10. Recruitment and 11. informed consent 12. Suitability of investigator 13. Site suitability	Template links updated to UK versions of the template documents and to confirm that the EU harmonised versions are also accepted	3.3	11.2.20
13.Site suitability	Remove requirements for information to be submitted for NHS sites	3.3	11.2.20
13. Site suitability	Confirm that either the HRA form or the EU harmonised from can be submitted	3.2	3.2.20

10. Recruitment and 11. informed consent	Refer to the EU harmonised template being strongly recommended Confirmation that documents approved by the generic review group should not be submitted for review by the REC	3.2	3.2.20
1. Cover letter	To include details of patients and public involvement. This is based on significant feedback from Research Ethics Committees that is important information for the ethical review process.	3.0	7.10.19
6. IMPD	Should be a single document rather than separate documents where possible	3.0	7.10.19
6. IMPD	All information referred to in the IMPD, e.g. TSE certification, should be included in the IMPD document in the relevant section.	3.0	7.10.19
12. Suitability of the investigator	Clarification of requirements and link to CV and declaration if interest templates	3.0	7.10.19
13. Suitability of the site	Clarification of requirements for NHS sites	3.0	7.10.19
1. Cover letter	Wording has been included to give greater emphasis to the importance of this document as part of the REC review process and in particular to include a summary of the trial which is written in language understandable to a lay person.	2.2	15.3.19
2. Protocol	Wording has been included to give greater emphasis to the importance of this document as part of the REC review process and in particular to include a summary of the trial which is written in language understandable to a lay person.	2.2	15.3.19
10. Recruitment arrangements	Added to say that details of how potential participants will be included should be included.	2.2	15.3.19
12. Suitability of the investigator	Updated to say that for non NHS/HSC trials, the CV of the principal investigator(s) should be submitted and for NHS trials, the same process as for other CTIMPs should be followed.	2.2	15.3.19
13. Suitability of the facilities	Updated to say that there is a site suitability template available on the website which can be completed instead of the IRAS SSA form for non NHS/HSC trials. However, the IRAS SSA form will continue to be accepted also.	2.2	15.3.19
15. Financial and other arrangements	Updated to confirm what should be provided where the sponsor has appointed a legal representative.	2.2	15.3.19