Version 5.0 of the NRES SOPs – summary of main changes

TOPIC	REFERENCE	CHANGE
Introduction and scope to the SOPs		
GAfREC	Paragraph 2	The SOPs are issued by NRES under the harmonized edition of the Governance Arrangements for Research Ethics Committees (GAfREC) published by the UK Health Departments in May 2011 and scheduled to come into effect on 1 September 2011.
Application of the SOPs	Paragraph 4	The SOPs apply to all RECs within the UK Health Departments' Research Ethics Service established under GAfREC. These RECs are listed in paragraph 4 and now include the Gene Therapy Advisory Committee (GTAC). To enable GTAC to adopt the SOPs, adaptations have been made where necessary to take account of special provisions for gene therapy trials in the Clinical Trials Regulations, e.g. the 90 day timeline for applications, and the procedures for GTAC appeals under Regulation 16 and Schedule 4.
Section 1: Applications		
Flagged RECs	1.7 - 1.15	These paragraphs describe a revised policy on review by flagged RECs. Review by a flagged REC is mandatory where legal or regulatory requirements apply, and in the case of certain research reviewed by GTAC. Otherwise, while allocation to a flagged REC is strongly recommended to applicants, review by a flagged REC remains optional.

Remit of GTAC	1.18 – 1.21	Sets out the remit of GTAC. As well as trials which must be submitted to GTAC under the Clinical Trials Regulations, GTAC is the national flagged REC for other trials of advanced therapy medicinal products and certain other types of research.
Remit of the AAPEC RECs	1.22 – 1.23	Clarifies the remit of the RECs appointed by the Appointing Authority for Phase 1 RECs.
Remit of the Social Care REC	1.26 – 1.28	Summarises the remit of the Social Care REC (set out in full in Annex K). As well as its core business, the Social Care REC may review research involving the NHS where the study is based on social sciences methodology and there are no clinical interventions or changes to the care of NHS patients.
Remit of MoDREC	1.29 – 1.30	Summarises the remit of the two RECs comprising MoDREC. Although MoDREC is not formally part of the UKHDs' Research Ethics Service, it is recognised as operating to equivalent standards. The SOPs clarify that further REC review is not normally necessary where MoDREC has given a favourable opinion on a study within its remit.
Booking and submission of applications	1.32 – 1.39	Revised procedures anticipating the introduction of electronic submission arrangements for all applications – to be implemented following testing of IRAS functionality. In the meantime, the previous SOPs will continue to apply. Following introduction of e-submission, no paper copies of any application documentation will be required and should not be accepted by REC offices except where technical problems arise and the submission is urgent. Use of booking checklists by Co-ordinators is now standard procedure.
Validation criteria	1.40 – 1.63	Use of validation checklist by REC office is now standard procedure. (1.44). Following introduction of e-submission, all documentation must be submitted electronically as part of a valid application. Relevant declarations must have electronic

		authorisation in IRAS. An ink signature will no longer be required by the Chief Investigator on a CTIMP application. (1.45(a),(d)) Validation criteria for non-CTIMP now include requirement for a legal representative based in the UK where a sponsor or co-sponsor is based outside the UK, to comply with the Research Governance Framework. (1.45(l)). Special procedures apply to validating applications for review under the Proportionate Review Service. (1.57-1.62, see also Section 8)
Transfer of applications	1.64 – 1.78	Mainly consequential changes related to introduction of e-submission.
Revised application forms	1.85 – 1.88	New guidance is included, setting out a limited range of circumstances where submission of a revised application form may be required. In general, such revision is <u>not</u> required to provide additional information or clarification to the REC during the ethical review; this should normally be provided in correspondence. The guidance also explains how applicants can update their IRAS dataset at any time.
Applications outside the remit of the REC	1.90 – 1.93	Under GAfREC, research is within REC remit where there is any legal or policy requirement for REC review, not only where the research involves NHS patients. (1.90) Under GAfREC, research involving the staff of health or social care services, or healthcare market research, does not normally require REC review but applications may exceptionally be accepted by the Research Ethics Service where significant ethical issues arise. Decisions on such applications will be made by REC operational managers. (1.91) RECs continue to have discretion to accept other applications where there is no legal or policy requirement for REC review and the applicant has no alternative source of ethical review, e.g. from a university REC. (1.93)
Projects not considered to be research	1.94 – 1.96	Revised guidance on requests for pre-application advice on whether a project is research.

		Where a project is submitted as research, it should be validated and reviewed as research by the REC.

Section 2: Full meetings of a REC		
Submission deadlines for applications	2.7	Currently a REC may set deadlines for submission of applications within a range of 7-21 days prior to the meeting. 14 days is now the usual operating practice for most RECs and this will become the SOP for most applications. Exceptionally, a REC may set an earlier deadline where a 90 day or longer time limit applies to the ethical review, e.g. for gene therapy and somatic cell therapy trials, allowing more time to consult referees before the meeting on complex applications where necessary.
Number of applications on the agenda	2.12	Currently a REC is expected to review between 5 and 8 applications at a full meeting. The revised SOP states that a REC will normally be expected to review around 6 applications per meeting. This takes account of the introduction of proportionate review, which will involve additional sub-committee work for members and also mean that full meetings will normally be reviewing applications raising more significant issues.
Distribution of papers	2.22	Linked to the change to 2.7, the final deadline for distribution of papers to REC members is now 10 calendar days prior to the meeting.
Attendance of Chief Investigator and sponsor	2.24	Drafting changes to indicate that attendance of a sponsor's representative at the meeting alongside the Chief Investigator is welcomed.
Quorum	2.35, 2.44	Operational managers may permit attendance of members by tele-conference or video-conference in exceptional circumstances. Such attendance counts towards the quorum requirement.
Co-opting to GTAC	2.40	Under the Clinical Trials Regulations, persons co-opted to meetings of GTAC are not required to be members or ex-members of other RECs.
Declarations of interest	2.58-2.62	Includes a definition of what constitutes a 'material interest' and should be declared, recorded and managed appropriately by the committee.

Section 3: Giving an ethical opinion		
Time limits for ethical review	3.1-3.6	Sets out a policy aim that, for research subject to a 60 day limit and reviewed in full committee, opinions will normally be given within 40 days (not including time taken to respond to one request for further information as part of a provisional opinion). For applications reviewed in sub-committee under proportionate review (see Section 8), the aim is for the opinion to be issued in 14 days. Clarifies that a 90 day time limit applies to review of clinical trials of gene therapy medicinal products (by GTAC).
Decisions available at a full meeting	3.8, 3.47-3.51	The 'no opinion' decision has been rarely used by RECs. It creates operational difficulties as there is a statutory requirement for the application to be re-considered and an opinion given at a full meeting, with a risk of missing the 60 day deadline. Instead, RECs may give a 'provisional opinion pending consultation with a referee', but will defer the formal request for further information until the advice of the referee is available. The clock will then stop at this point. Following receipt of the further information, the opinion can be confirmed by Chair or sub-committee.
Decisions available to a sub-committee undertaking proportionate review of a new application	3.8, 3.12-3.13, 3.16, 3.37, 3.52-3.54	SOPs for decision-making under the Proportionate Review Service are incorporated within the SOPs, based on experience from the pilot scheme. Decision options are the same as in full committee, except that: • An unfavourable opinion may only be given for very poor quality applications • 'No opinion' may be given and an application referred to full committee for further review of significant ethical issues.
Unfavourable opinion based on safety issues in a CTIMP	3.33	Reflects provision in Version 2 of the Memorandum of Understanding with the MHRA that a REC should not give an unfavourable opinion based on safety issues in a CTIMP without first consulting the MHRA Clinical Trials Unit.

Notifying the MHRA of reasons for an unfavourable opinion in a CTIMP	3.34	Incorporates operational procedures introduced in March 2011 to notify MHRA of reasons for unfavourable opinions, using the fields prescribed by the Commission, for upload into EudraCT. The fields are listed in Annex E.
Communications with the applicant	3.17, 3.43	Letters should include a contact point for requests for further clarification from the applicant. Where the response to a provisional opinion is inadequate, it is recommended that the applicant is contacted directly to discuss the outstanding issues.
Regulatory approval	3.55 *[3.47-3.57 and 3.80-3.93 of v.4.1 of SOPs]*	Detailed guidance on issues around parallel applications for regulatory approval is transferred to the new Section 13.
Insurance, indemnity and compensation	3.56 *[3.58-3.75 of version.4.1 of SOPs]*	Detailed guidance is transferred to Annex G.
Variation of opinion	3.60-3.64	Provision is included to allow a REC to vary an opinion where it emerges that it is based on factual error or misunderstanding. The CI or sponsor may request variation of opinion by writing to the REC Chair, copied to the operational manager.
Corrective action following a legally invalid opinion on a CTIMP	3.65	Annex D includes the procedures agreed in the Memorandum of Understanding with the MHRA for corrective action where it emerges that the REC opinion is not valid because of non-compliance with the procedural requirements of the Clinical Trials Regulations.

Section 4: Site-specific assessment		
Requirement for SSA at non-NHS sites	4.5	The requirement for SSA for "other clinical trials or investigations" is modified to restrict this to clinical trials involving novel interventions or randomised clinical trials. This is linked to a modification of the IRAS Project Filter to distinguish between interventional clinical trials and "basic science studies", not involving novel interventions, which do not require SSA and also justify a reduced dataset in IRAS.

Non-NHS sites	4.19	
Definition of a site	4.19 4.20, 4.30	'Social enterprise' is added to the list of examples of non-NHS sites. Employee-led social enterprises may deliver health and social care within the NHS but are not NHS organisations. Further guidance is provided to clarify that where NHS and non-NHS facilities on the same premises are managed as a joint site under the Research Governance Framework and indemnity is in place, this may be regarded as a single NHS site. The implication is that separate SSA of the non-NHS facilities (or SSA exemption) is not required as this will be included within the review undertaken by the R&D office.
Electronic submission	4.33, 4.36	Following implementation of e-submission from IRAS, all SSA applications for non-NHS sites will be submitted electronically.
Issues reviewed in SSA	4.39	For SSA at non-NHS sites conducting CTIMPs, issues relating to pharmacy support are included within the scope of SSA.
Delegation of SSA for non-NHS sites	4.68-4.69	Reinstates the process to allow delegation of SSA for non-NHS sites to another body.

Section 5: Amendments		
Amendments to include adults lacking capacity	5.8	Exceptionally, 60 days is allowed for review of such amendments and the clock may be stopped once (non-CTIMPs only).
Substantial amendments submitted alongside or during initial application	5.11	The circumstances in which this is permitted have been widened, and the provision applies to non-CTIMPs as well as CTIMPs.
Substantial amendments to CTIMPs	5.5, 5.17, 5.20-5.23, 5.34-5.36	Substantial amendments to CTIMPs not requiring ethical review no longer need to be notified to the REC for information, in line with revised guidance from the European Commission.

		Guidance on the types of substantial amendment reviewed by MHRA and/or the REC has been revised in line with the latest version of the European Commission guidelines (see Annex C).
Electronic submission	5.15	Following implementation of e-submission from IRAS, all notices of substantial amendment (NOSA) will be submitted electronically.
Validation criteria for NOSA	5.22(c)	An authorised declaration from the sponsor's representative will be required for substantial amendments to non-CTIMP studies using the NRES NOSA form in IRAS. (For CTIMPs, signature by the sponsor's representative is already included on the European Commission Annex 2 form.) This will ensure that the sponsor is aware of and supports all planned substantial amendments, for which they are ultimately responsible.
Responsibility for deciding whether an amendment is substantial	5.26-5.27	The current position is that it is the sponsor's responsibility to determine whether an amendment to a CTIMP is substantial and requires notification, but the REC's responsibility for other studies. A consistent policy is now adopted under which the sponsor is responsible in all cases. The Research Ethics Service will continue to advise sponsors where requested on whether amendments should be considered substantial.
Guidance on amendments typically considered substantial or non-substantial	5.30-5.31	This general guidance has been slightly modified. For detailed guidance on amendments to CTIMPs, refer to Annex C.
Appeals	5.54-5.59	A procedure is introduced for appealing against an unfavourable opinion. The opinion remains the responsibility of the main REC, but the matter is reconsidered at a full committee meeting and the REC should give due consideration to the applicant's representations and advice from other sources, including the opinion of a second REC.

Section 6: Sub-committees		
Proportionate review of new applications	6.3-6.4, 6.10, 6.12, 6.23-6.25	Incorporates sub-committee procedures for proportionate review of new applications, based on the pilot scheme.

Co-opting of members	6.27	Where a sub-committee is not undertaking CTIMP business, up to 2 members may now be co-opted. (For CTIMPs, the Regulations allow only one co-opted member.) In the case of standing sub-committees established by REC centres to undertake proportionate review under paragraph 6.12, the sub-committee may include more than 2 members from RECs other than the REC of the chairperson ("the host REC".

Section 7: Further review following an unfavourable opinion		
Options following an unfavourable opinion	7.1	Cross-reference to the option to request a variation of opinion (see 3.60-3.64).
Appeals against unfavourable opinions by GTAC	7.36-7.53	Sets out provisions for appeals to GTAC in the case of unfavourable opinions on CTIMPs, taking account of the special provisions under the Clinical Trials Regulations. Where GTAC gives an unfavourable opinion on a non-CTIMP, the usual provisions for appeal to a second REC will apply.

Section 8: Expedited and proportionate review		
Proportionate review	8.2-8.3 8.13-8.16	Version 5.0 of the SOPs includes for the first time procedures for expediting the review of applications which do not raise significant ethical issues. Paragraphs 8.2-8.3 summarise the overall policy. The detailed procedures are incorporated within other relevant sections of the SOPs (see list of references at paragraph 8.16). These procedures are based on those developed and evaluated by NRES in the pilot scheme which started in London in 2009 and has since been extended to a number of other REC centres. Criteria for determining whether studies are suitable for proportionate review are developed with advice from the National Research Ethics Advisers' Panel. Proportionate review will become a routine feature of NRES business at all REC centres in England. The timing of implementation will depend on operational factors in each

		centre. Pilots are also underway in Scotland, Wales and Northern Ireland.
Research in a public health emergency	8.5-8.12	Includes the criteria which will be used by the Research Ethics Service and other regulators to determine whether research applications should be expedited in a public health emergency. Decisions on expediting applications will be shared with other bodies to facilitate a co-ordinated approach.

Section 9: Monitoring research with a favourable opinion		
Commencement of the study	9.9	Studies abandoned before starting should be notified to the REC by letter rather than on the declaration of end of study form.
Duration of the study	9.11	Further guidance included to emphasise that in the case of studies involving human tissue in England, Wales or Northern Ireland, authority to store "relevant material" under the ethical approval for a specific project expires when the original project ends.
SUSAR reports	9.25-9.36	Updated guidance to reflect the revised guidance on safety reporting from the European Commission (CT-3, revision dated June 2011). In particular, SUSAR reports should be in the ICH E2B format which is now the standard for clinical trials.
Annual safety reports	9.37-9.44	Updated guidance to reflect the revised Commission guidance. In particular, from 1 September 2011 all ASRs must be in the format for Development Safety Update Report (DSUR) set out in the ICH E2F guidance. The outline format for DSURs is set out in Annex F to the SOPs for reference by Co-ordinators and RECs.
6 monthly safety reporting	*9.39 (in version 4.1 of SOPs)*	Requirement for a 6 monthly safety report in commercially sponsored CTIMPs with sites outside the UK has been removed in line with the revised Commission guidance.
Final safety report for first-in-human Phase 1 trials	9.50	Requirement for a final safety report to be included with the end of trial declaration for a FIH Phase 1 trial has been removed in line with the revised Commission guidance.

Submission of safety reports to the REC	9.52	Safety reports (together with the standard cover sheet) should be sent by email rather than hard copy by post.
Protocol deviations and violations	9.72-9.75	Further guidance to clarify the distinction between protocol deviations and protocol violations. For revised guidance on notifying the REC of protocol violations meeting the criteria for "serious breaches", see paragraphs 9.107-9.118.
End of study	9.79-9.86	Further guidance is given on the definition of the end of the study. Procedures for declaring the end of trial in a CTIMP are aligned with the latest guidance from the European Commission. Where a trial is conducted in more than one Member State, it is only necessary to submit one end of trial declaration when the whole trial has ended, rather than individual declarations for each country. At the sponsor's discretion, the REC and the MHRA may be notified by letter or email when the UK trial has ended.
Suspension and termination of opinion in a non-CTIMP	9.87-9.101	The procedures have been reviewed with a view to ensuring due process. Except where immediate action is justified, a REC should issue a Notice of Intention to Suspend or Terminate a Favourable Opinion prior to suspending or terminating an opinion, giving the sponsor opportunity to address issues of concern or make representations. (A template for the NISTFO will be available in RED.) Where an opinion is suspended, this should be kept under review by the REC. Provision is made for appeal by the sponsor.
Review of opinion in a CTIMP	9.102	Current guidance is transferred to the new Section 13 on communications with other bodies.
Transfer of main REC responsibility	9.124	New paragraph setting out the circumstances in which the responsibilities of main REC may be transferred to another REC.

Section 10: Research databases
Section 10 previously set out the transitional procedures applying to review of CTIMPs which pre-dated the implementation of the Clinical Trials Regulations in 2004. In particular they described arrangements for appointing a main REC for a study originally reviewed by more than one REC. These arrangements are relevant only to a small number of long-running trials, all of which will now have well-established arrangements for continuing review by a nominated main REC. The procedures have therefore been omitted from version 5 of the SOPs. Any queries in future may be referred to the NRES Head of Operations.
In this version of the SOPs, Section 10 now covers guidance on the ethical review of research database applications. The SOPs are based on, and supersede, the interim guidance issued by NRES in 2008 (see http://www.nres.npsa.nhs.uk/applications/guidance/research-guidance/?esctl1428681_entryid62=66997). They also take account of the 2010 report by a Working Group on Research Databases established by the National Information Governance Board.

Section 11: Research involving human tissue		
Validation criteria for research tissue bank (RTB) applications	11.24	All applications to be submitted electronically following implementation of e-submission from IRAS. Applicant CV to be included with applications. (Also applies to research databases – see paragraph 10.16).
Annual progress reports by RTBs	11.30(e)	A specific template for the annual report will be available on the NRES website and should be used by RTB managers. (A similar template will be provided for research databases – see paragraph 10.27(h).)
Renewal of approval	11.33-11.36	Sets out a revised procedure for 5 year renewal of ethical approval. (A similar procedure will apply to renewals of database approvals – see paragraphs 10.35-10.38).

Section 12: Research involving adults lacking capacity		
Flagged RECs	12.22, 12.24	It is no longer mandatory for applications under the Mental Capacity Act to be reviewed by a flagged REC, though this continues to be recommended and will be the normal allocation by CAS. For general policy on flagging, see paragraphs 1.7-1.15.
Substantial amendments to include adults lacking capacity in a non-CTIMP	12.61-12.64	Revised guidance specifying that such amendments should be reviewed at a full meeting and are subject to a 60 day timeline. Specific guidance applies to such amendments in Scotland (see 12.64).

Section 13: Communications with other bodies
New section collating SOPs relating to sharing of information and collaboration with other regulatory bodies undertaking review of research in parallel with REC review. *Existing SOPs relating to communications with MHRA have been transferred to this section from Sections 3 and 9.* *Additional material has been added on communications with the National Information Governance Board (NIGB) and the Administration of Radioactive Substances Advisory Committee (ARSAC), based on agreed arrangements with those bodies.*

Section 14: Retention of documentation
New section collating requirements for retention of application documentation by RECs, based largely on existing operational guidance.

ANNEXES

Topic	*Version 4.1*	*Version 5.0*	*Comments*
Index to standard letters and forms	Annex A	Annex A	
After ethical review – guidance for sponsors and investigators (CTIMPs)	Annex B	-	Omitted from the SOPs. Available separately on the NRES website.
After ethical review – guidance for sponsors and investigators (non-CTIMPs)	Annex C	-	Omitted from the SOPs. Available separately on the NRES website.
Guidance from the European Commission on substantial amendments	Annex D	-	Omitted from the SOPs. Available separately on Commission website.
Notification of substantial amendments to CTIMPs	Annex E	Annex C	This annex identifies the types of substantial amendment to CTIMPs normally requiring review by the MHRA or the REC, or by both bodies, or not requiring notification. It has been rewritten in the light of the revised European Commission CT-1 guidance.
Definition of a CTIMP	Annex F	Annex B	
Corrective procedures following a legally invalid ethical opinion on a CTIMP	-	Annex D	New Annex based largely on procedures in Appendix E to Version 2 of the Memorandum of Understanding between MHRA and the Research Ethics Service.
Regulatory requirements for clinical investigations of medical devices	Annex G	-	Relevant material is now included with the guidance in Section 13 on communications with MHRA Devices Division.
Notification of reasons for unfavourable opinion in a CTIMP to the MHRA	-	Annex E	

Format and content of annual safety reports on CTIMPs	-	Annex F	Summarises the template headings for ASRs based on the format for DSURs under ICH E2F – see paragraph 9.37.
Insurance, indemnity and compensation	-	Annex G	New annex based largely on existing SOPs transferred from Section 3. *[Additional guidance to be included on insurance for Phase 1 trials, based on guidelines developed by an industry task force to be published shortly.]*
Statutory requirements for regulation of research involving human tissue	Annex H	Annex H	
Research tissue banks – approval conditions	Annex J	-	Omitted from the SOPs. Available separately on the NRES website.
Gene Therapy Advisory Committee	Annex K	Annex J	Now includes more detailed guidance on the remit of GTAC.
Research databases – approval conditions	Annex L	-	Omitted from the SOPs. Available separately on the NRES website.
Social Care Research Ethics Committee		Annex K	New annex setting out detailed guidance on the remit of the Social Care REC.
Responsibilities of REC operational managers in England	-	Annex L	New annex setting out levels of delegated responsibility within NRES for decisions and actions under SOPs.