

Integrated Research Application System (IRAS)

Collated Question-specific guidance for IRAS Form

The following document collates all guidance for the questions in IRAS Form.

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Part B Section 3: Ionising Radiation

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PART A: Core study information

The short title of the research

- The program automatically uses this to create a "header" throughout the form. The applicant should include a version number as part of the short title to help the identification of documentation approved and the future monitoring of the application.
- Use this title consistently in all information sheets and consent forms for research participants or others giving consent on their behalf. It must be sufficiently detailed to make clear to participants what the research is about. If acronyms are used the full title should explain them.

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Submission date

- Insert the date on which you intend to submit an application on each application form generated by IRAS.
- For the REC application, the submission date should be agreed with the NRES Central Allocation System or the REC office when you book the application.

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Question A1 - Title of the research

- The full title should be consistent with that on any documents submitted for regulatory purposes, e.g. to the Medicines and Healthcare products Regulatory Agency (MHRA).
- You are expected to enter a full title.

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Educational projects

- According to section 9.3 of the UK Policy Framework for Health and Social Care Research, students should not normally take the role of Chief Investigator at any level of study, as this function should be undertaken by supervisors or course leaders.
- Exception is made for an experienced care practitioner or manager undertaking an educational qualification for continuing professional development or a doctoral-level study while employed by a health and social care provider or university, or for a researcher undertaking a doctoral-level study in receipt of a fellowship.
- Where acting as the Chief Investigator, the academic supervisor should sign both the Chief Investigator and supervisor declarations.
- A copy of a current CV for the student(s) and the academic supervisor(s) (maximum 2 pages of A4) should be submitted with the application.

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Question A3-1 - Chief Investigator (CI)

- This is the person designated as taking overall responsibility within the team of researchers for the design, conduct and reporting of the study.
- For research within the responsibilities of the UK Health Departments, the responsibilities of Chief Investigators are described in the UK Policy Framework for Health and Social Care Research available: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/>
- For international studies with a chief or "co-ordinating investigator" outside the UK, the form should name as CI the investigator who will take responsibility for the study within the UK.
- For CTIMPs, the CI must be a health professional as defined in the Medicines for Human Use (Clinical Trials) Regulations 2004. This means a person registered in the UK as a doctor, dentist, nurse or pharmacist.
- For multi-site CTIMPs sponsored by a pharmaceutical company, the CI can be an employee or contractor of the company. However this should be a health professional with current relevant experience. For single-site CTIMPs, the CI must be the Principal Investigator at the site.
- For research funded by a grant the CI should normally be the grant-holder.
- Any subsequent change in the CI should be notified to the REC as a substantial amendment. A favourable opinion from the REC is required for such a change.
- Ensure you enter data in the fields for:
 - ◊ Given name (CTIMPs) or Forename/Initials (non-CTIMPs)
 - ◊ Family name (CTIMPs) or Surname (non-CTIMPs)
 - ◊ Post (non-CTIMPs)
 - ◊ Employer (non-CTIMPs)
 - ◊ Institution name (CTIMPs)
 - ◊ Street address (first line)(CTIMPs) or Work address (first line)(non-CTIMPs)
 - ◊ Town/city (CTIMPs)
 - ◊ Post-code
 - ◊ Country
 - ◊ work email address
 - ◊ work telephone

- A CV for the CI should be submitted with all applications. The CV should be in summary form, with only information relevant to the current application. For example, it should give evidence of previous research in the same field of study, and other relevant experience and training. The length should be a maximum of 2 pages of A4. It is recommended that applicant use the CV template available on IRAS.

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Question A3-2 - ORCID ID

- ORCID is being integrated into the manuscript submission process by publishers and several funders, such as the NIHR, plan to use it to streamline the research management process. An ORCID ID will belong to a researcher throughout their research career as a unique, persistent identifier that, over time will reduce repetitive entry of biographical and bibliographical data in multiple systems whose funders are also ORCID members. More information is available here <http://orcid.org/>

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Question A4 - Central study coordinator

- Please enter details of the person who should receive all correspondence relating to applications for this project in addition to the Chief Investigator.
- This contact may be the Sponsor, a Project Manager, Trial Manager, Clinical Research Scientist or Study Coordinator. Where a Contract Research Organisation (CRO) has been delegated to handle applications on behalf of the sponsor, the contact at the CRO should be named here.
- Ensure you enter data in the fields for:
 - ◊ Forename/Initials
 - ◊ Surname
 - ◊ Address (first line)
 - ◊ Post-code
 - ◊ Email address
 - ◊ Telephone

- Please note that this field does not apply to applications to MHRA.

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Question A5-1 - Reference numbers

- This question is largely administrative. It is useful to have all reference numbers recorded in one place.
- If one of the reference numbers listed is not applicable to your study state N/A. Please note that you are expected to enter a reference number in the funders reference number field. If this type of reference number is not applicable to your study then you are expected to enter 'N/A in the field'.
- If the project has a website, give the URL.
- Any translation of the protocol should be assigned the same date and version as those in the original document.

Policy and guidance for registration of clinical trials

- The Declaration of Helsinki of the World Medical Association (revised 18 October 2008 at Seoul) states:
"19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."
- The World Health Organisation (WHO) regards trial registration as the publication of an internationally agreed standard dataset about a clinical trial on a publicly accessible database managed by a registry conforming to WHO standards. The standard dataset is published by the WHO International Clinical Trials Registry Platform (ICTRP) at <http://www.who.int/ictrp/network/trds/en/index.html>.
- The International Standard Randomised Controlled Trial Number (ISRCTN) is a simple numeric system for the unique identification of clinical trials worldwide. It will simplify the identification of trials and provide a unique number that can be used to track all publications and reports resulting from each trial. For more details go to: <http://www.isrctn.com/>
- Alternatively, trials may be registered at <http://clinicaltrials.gov>.
- The EudraCT number is the mandatory reference number allocated by the European

Medicines Agency (EMA) for CTIMPs authorised on or after 1 May 2004. Further details can be found from the EMA at <http://eudract.emea.europa.eu>. Please note you must enter this reference number if your project is a CTIMP.

- It is government policy in the UK to promote registration of clinical studies and public access to research findings affecting health and social care. For more information see <http://www.dh.gov.uk/en/Researchanddevelopment/A-Z/Researchgovernance/index.htm>.

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Question A5-1 - Options for registration

- The EudraCT number is the mandatory reference number allocated by the European Medicines Agency (EMA) for CTIMPs authorised on or after 1 May 2004. Further details can be found from the EMA at <http://eudract.emea.europa.eu>.
- The International Standard Randomised Controlled Trial Number (ISRCTN) is a simple numeric system for the identification of clinical trials worldwide. The ISRCTN Register accepts the registration of randomised controlled trials and any other research study designed to assess the efficacy of health interventions in a human population. This includes both observational and interventional studies. The Register provides a unique number that can be used to track each trial throughout its lifecycle from initial protocol to publication of results. For more details go to: <http://www.isrctn.com/>
- Alternatively, clinical research may be registered at <http://www.clinicaltrials.gov> (a register of studies in the United States and around the world) or through the metaRegister of controlled trials at http://www.controlled-trials.com/mrct/mrct_about.
- For other types of research, registration is also encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details in the "Other Reference Number(s)" section. If not, you may indicate that no suitable register exists.
- In general, registration is not expected for projects undertaken entirely for educational purposes below doctoral level.

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- Alternatively, clinical research may be registered at <http://www.clinicaltrials.gov> (a register of studies in the United States and around the world) or through the metaRegister of controlled trials at http://www.controlled-trials.com/mrct/mrct_about.
- For other types of research, registration is also encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details in the "Other Reference Number(s)" section. If not, you may indicate that no suitable register exists.
- In general, registration is not expected for projects undertaken entirely for educational purposes below doctoral level.

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Question A5-2 - Links with previous studies or other applications

- If this research is a follow-up study to a previous or current application by the Chief Investigator, or if the application is part of a series of closely linked projects in a programme, give details of relevant previous or current applications. This information will allow reviewers to access relevant background information if required. Please do not list all past and current applications unless directly relevant to this application.

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Question A6-1 - Summary of the study

All applications should enter a research summary in the free text box provided.

Writing the research summary

- Your answer to this question should be a short summary of the proposed research (maximum

300 words) written in plain English. Where technical terms are used they should be explained. All acronyms should be described in full.

- The title should be concise and include the condition under study, the treatment being evaluated and the group to be recruited, framed as a research question.
- The summary should then briefly describe the background to the research, why it is important, the questions it will answer and potential benefits, the study design and what is involved for participants, who is funding the research and where it will be recruiting.
- Questions you may wish to cover in writing the summary:

- Why? What research question is being addressed?
How is it of relevance and importance to patients and public?
- What? Broadly what area (disease, therapy or service) is being studied?
For therapeutic studies what is the drug, device or procedure being tested.
- Who? Who would be eligible?
- Where? The type of sites where the study will be conducted.
- How? How long will the study last and what will the participants undergo?

- This summary should be suitable for the public, patients wanting more information about their condition, researchers reviewing current literature and doctors planning treatment. Given its size, we recognise it cannot be comprehensive and will need compromise to meet all audiences. Rather it will be a "signpost" and any reader wishing more information will need to seek further details.
- Applicants are advised to exclude information from the summary where exemptions apply under the Freedom of Information (FOI) Acts (e.g. if disclosure of the information is likely to harm commercial interests, or pose a risk to health and safety of any person, or if the information includes personal data).
- The REC may comment on the summary in the course of the ethical review. For example, it may suggest changes to make the summary more comprehensible or informative for patients and public. However, any such suggestions will be given separately from the ethical opinion on the research and may be regarded as non-binding advice from the committee. The content of the summary will not determine the committee's opinion.

Publication of research summaries

- The interests of the public, patients, research participants and researchers are best served by open research and, recognising this, international bodies, medical journal authors and researchers have promoted trial registration. For example, the World Health Organisation (WHO) states on its website (<http://www.who.int/ictrp/en/>):
"The mission of the WHO Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will...ultimately strengthen the validity and value of the scientific evidence base."

- The UK Research Ethics Service (UK RES) shares this view and believes that open research is ethical research. UK RES publishes summaries of all REC applications, together with the ethical opinion. In the case of medicinal trials (CTIMPs), an ethics committee is legally required to publish a summary of its opinion by Regulation 15(9) of the Clinical Trials Regulations. This is also required by the Governance Arrangements for NHS Research Ethics Committees (GAfREC) for all types of application reviewed by RECs.
- Publication of research summaries and opinions will also support compliance with requirements under Freedom of Information legislation to publish information held by public bodies.

Content of the published research summary

- The published summary will be produced from information provided by applicants in answer to the following questions:

Summary	A6-1
Study design	A7
Disease/diagnosis	A15
Timescale and duration for participants	A21 and A69
Details of trial registration	A5-1 and A50
Contact point for further details	D1

- Publication of a contact point will be subject to agreement by the applicant. For further information, please refer to the guidance in the Declaration section at D1.

Arrangements for publication

- Research summaries will be published for all applications submitted from 1 May 2008.
- Publication of research summaries will be on the Health Research Authority (HRA) website at <http://www.hra.nhs.uk>. Publication will take place no earlier than 3 months following the issue of the committee's final opinion (or the withdrawal of the application). HRA will write to the Chief Investigator in advance and provide a copy of the intended text for publication. Contact details will only be included in the summary with explicit permission.
- HRA also plans in future to publish summaries of the ethical opinion and is currently exploring the best way of producing the summary. The arrangements will *not* apply retrospectively to applications already concluded at the time of implementation.
- For further information please see <http://www.hra.nhs.uk>.

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Question A6-2 - Summary of main issues

- This should be a discussion of the main ethical and design issues arising in the research, how you have addressed them and who you have consulted in developing the proposal.
- You may have made choices when designing your study. Explain the options you considered and the reasons for and against these, summarising why you finally settled on one. The reasons are as important as the final choice itself.
- Indicate any important information not covered elsewhere in the application, and any specific issues on which you would welcome advice from the REC.
- Where you have involved or sought advice from patient groups, carers, service users or members of the public with relevant experience or knowledge of the issues raised by this question, you should explain and clearly state how what they have said informed your approach to addressing these issues. You may also find it helpful to involve them in completing this question.
- The following paragraphs highlight key areas you may wish to address.

Purpose and design

- RECs pay particular attention to the purpose of a study, asking "*What question is the research asking, is it worth asking and can this proposal answer it?*". Justify the research, showing how it builds on existing knowledge. Summarise the key choices you have made in formulating the research questions and methodology.
- Indicate who has been involved in developing the research proposal, including scientific critique and input from patient or community groups.
- It is perfectly reasonable for one purpose of the research to be educational.

Recruitment

- Many different methods may be used. RECs will look carefully at the relationship between a potential participant and the "recruiter" to ensure this process is free from undue influence. Recruitment material should make few, if any, therapeutic promises, there should be no coercion or unacceptable inducement. Only very limited personal data should be collected at this stage.

Inclusion / exclusion

- No one should be unfairly excluded from or included in research. Choices made in both inclusion and exclusion criteria may require justification.

Consent

- Valid consent is underpinned by adequate information and the capacity of participants to decide for themselves. A capable person will:
 - Understand the purpose and nature of the research.
 - Understand what the research involves, its benefits (or lack of benefits), risks and burdens.
 - Understand the alternatives to taking part.
 - Be able to retain the information long enough to make an effective decision.
 - Be able to make a free choice.
 - Be capable of making *this particular decision* at the time it needs to be made.
- RECs increasingly ask "Can you, or whoever will seek consent, assess capacity and do you understand the ethical principles underpinning informed consent?"
- If research involves participants who are unable to represent their own interests or are particularly susceptible to coercion (vulnerable individuals), it will be important to explain why this research is needed and how their interests will be protected.
- If research is to be conducted without consent, this needs explanation and justification.

Risks, burdens and benefits

- Summarise and weigh up the risks/burdens and benefits, exploring both likelihoods and the consequences of harm. It helps to "put yourself in the participants" shoes" and try to imagine how he or she would see the project. If it is possible, discuss it with potential participants. This is an area where consultation with the community or patient groups could provide support.
- It is crucial you have worked to minimise risk and protect your participants and you should demonstrate this to the REC.
- If you are allocating participants to treatments, the committee will expect equipoise, and it will help your application if you summarise the arguments that indicate this.

Confidentiality

- The "Caldicott Principles" set out an ethical framework for use of identifiable data:

Principle 1 - Justify the purpose(s) for obtaining the information.

Principle 2 - Don't use person-identifiable information unless it is absolutely necessary.

Principle 3 - Use the minimum necessary person-identifiable information.

Principle 4 - Access to person-identifiable information should be on a strict need-to-know basis.

Principle 5 - Everyone with access to person-identifiable information should be aware of their responsibilities.

Principle 6 - Understand and comply with the law.

- Indicate any problems arising from the processing of identifiable data and/or tissue samples and say how they will be handled.
- Confidentiality is not "secrecy" and there may be (rare) occasions when this has to be broken. RECs expect confidentiality to be broken if participants or others are at serious risk. The possibility needs to be considered and the REC will wish to know how such an occasion will be managed.
- Where access to identifiable patient data is required without consent, an application should be made to Confidentiality Advisory Group (CAG).

Conflict of interest

- You should consider whether your interests as a researcher will conflict with your duties as a health care professional. If there is such a possibility, you will need to explain how it will be handled.
- What will happen at the end of your study?
- Consider carefully what will happen after your study has ended, particularly in the case of drug trials, and whether results will be fed back to participants.

Use of tissue samples in future research

- Samples should be used fairly, to the benefit of science and not to the detriment of donors. The idea of sample donations as a "gift" has stood the test of time and has support. Participants should know who will store the samples, for what purpose and who will have access.

For further guidance see:

<http://www.hra.nhs.uk>

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Question A7 - Methodology description

- Please tick all the descriptions that you feel apply to your project. This information is used by organisations to monitor the types of research activity taking place.

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Question A8 - Type of medicinal trial

- This question applies only to CTIMPs being conducted under the Medicines for Human Use (Clinical Trials) Regulations 2004.
- If the investigational medicinal product in your trial is a gene therapy product, you should apply to the Gene Therapy Advisory Committee (GTAC) as the main REC for the trial. In cases of doubt, please contact the GTAC Secretariat for advice. Contact details are at: <http://www.advisorybodies.doh.gov.uk/genetics/gtac/contact.htm>
- Some products may qualify both as medicinal products under the Medicines Act and medical devices. If so, you should draw this to the attention of review bodies and say which regulatory approvals are being sought. This is a complex area and advice may be sought from the MHRA Clinical Trials Unit by emailing clintrialhelpline@mhra.gsi.gov.uk. The MHRA will indicate whether application for regulatory approval of the trial should be made under the Clinical Trials Regulations or the Medical Devices Regulations. In exceptional cases, both sets of Regulations may apply.

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Question A10 - Research questions/objectives

- What question(s) are you trying to answer? Reviewers pay particular attention to the purpose of research, asking "What question is the research asking, is it worth asking and can it answer it?". Your answers should be succinct, excluding methodology, and realistic.

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Question A11 - Research questions/objectives

- What question(s) are you trying to answer? Reviewers pay particular attention to the purpose of research, asking "What question is the research asking, is it worth asking and can it answer it?". Your answers should be succinct, excluding methodology, and realistic.

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Question A12 - Scientific justification for the research

- RECs pay particular attention to purpose, asking "What question is the research asking, is it worth asking and can this proposal answer it?". RECs balance the potential benefits – whether for science, society or participants themselves - against the potential risks and burdens of the study.
- It therefore helps to place the study in context to demonstrate you are familiar with previous work and show how it will contribute to knowledge. Previous research should not normally be repeated where adequate evidence is already available.
- You should write your answer in a way that will be understood by lay members of the REC and other reviewers without relevant clinical or research expertise. Please avoid technical language. It is not acceptable to cut and paste from the protocol.
- The information provided should clearly and simply answer the following questions:
 - Why is the research considered worth doing and what will be gained by undertaking the project? Does it deepen understanding of disease/illness? Does it answer an important question?
 - What are the main research question(s) designed to answer - i.e. what is the "knowledge gap" the research is designed to fill?
 - What new information will the research provide?
 - Has similar research on this topic been done before?
 - In the case of student research, what training will it provide in research methodology?
- It is the applicant's responsibility to check the originality of the proposal, using all existing sources of evidence. Where research is to be repeated, this should be justified. Repeating research that puts participants at more than minimal risk may be considered unethical if the answer to the scientific question is already known from previous studies.

- It is recognised that *student research* has an educational and training value, and proposals (especially from undergraduates) will not normally be of the same originality or scientific importance as those submitted by professional researchers. However, applications from students should demonstrate knowledge of the relevant scientific background and the methodology to be used, and identify clear and realistic project objectives. Student proposals will be subjected to the same standard of ethical review as all other research proposals.

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Question A13 - Design and methodology

- After reading the answer to this question, a reviewer should have a clear overview of the research protocol or project plan, in particular a complete picture of what will be expected of participants. It helps to put yourself in the participant's shoes and try to imagine how he or she would see the project. If possible, discuss the design with potential participants or patient groups, carers, service users or members of the public with relevant experiences or knowledge.
- Depending on the type of research undertaken, the answer should include the following information:
 - ◊ The null and any alternative hypotheses and why such an alternative hypothesis was chosen.
 - ◊ Why the study design and methodology has been chosen and what has influenced the choice.
 - ◊ The justification for including control arms to a trial, if applicable. Particular justification should be given for use of a placebo arm. In a trial involving allocation to treatments, the REC will expect equipoise - summarise the arguments that indicate this.
 - ◊ The broad timetable for the stages of the research e.g. preparation, convening meetings/conducting interviews, interpreting and analysing findings, preparing the final report.
 - ◊ Where any interviews will take place.
 - ◊ Whether there will be planned interim analyses/reports.
 - ◊ What procedures will be in place to detect and compensate for any possible "researcher effects" and "researcher bias".
 - ◊ The details of any observational components of the research methodology and how

these will be carried out.

- The sampling and sample sizes for the project, including how participants will be identified, approached and sampled, and whether they are sufficient for the intended analysis.
- Where you have involved or sought advice from patient groups, carers, service users or members of the public you should explain how they helped to address the issues raised by this question and what changed as a result. It is helpful to demonstrate that people with relevant experience think that participants will understand and accept what will happen to them in the study. You may find it helpful to involve them in completing this question.
- It is important that the information given in this section clearly reflects the information set out in the protocol and in the Participant Information Sheet.

Additional guidance for research involving prisoners

- The answer to the question should reflect issues specific to prison populations, including in particular literacy levels, mental health needs and prisoner-staff relations.

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Question A14-1 - Patient/public involvement

- When patients, carers, service users and members of the public offer insights on their health condition or experiences to help researchers with the design and set-up of their studies, this is called Public Involvement in research. The UK health departments are committed to active public involvement in all stages of research. For more information see INVOLVE (<http://www.invo.org.uk/>) or, in Wales, see Involving People (<http://www.wales.nhs.uk/sites3/page.cfm?orgid=580&pid=14773>)
- This question does not refer to the involvement of patients, carers, service users or members of the public as participants in the research.
- You are expected to select at least one check box and use the free text box to give details of involvement, or if you have not and will not involve the public then you should use the free text box to set out your justification for the absence of involvement.

Where you have undertaken public involvement

In responding to this question, you should use the free text box to provide information about the patients, carers, service users or members of the public who have been involved designing the study and in what ways. Include the numbers involved and what they did when, as well as what experience they brought to the study and why that is relevant. Also include information about what the people you involved will do to help with the conduct, management and/or dissemination of the study.

As you are working through your application, you will come across questions where it will be helpful to include in your responses how the people described in A14-1 helped to address the issues raised by the questions and what changed as a result, either in the design of the study or in how it will be conducted, managed and disseminated. For example:

- A6-2: Summary of the main issues
- A13: Design and methodology
- A22: Potential risks and burdens
- A30-1: Informed consent
- A51: Dissemination of results and publication

If you worked with one or more patients, carers, service users or members of the public you can ask them to help you complete these questions in your application.

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Question A14-2 - Acceptability of using identifiable data without consent

- The Confidentiality Advisory Group (CAG) consider that evidence of patient involvement can help to demonstrate the public interest of an activity taking place and provide an opportunity to test the acceptability of the use of, and access to, confidential patient information without consent. Patients may also be able to suggest ways of recruiting participants, which may result in an application to CAG not being required as consent will be feasible.
- For these reasons CAG always consider what evidence has been provided that consultation has taken place with members of the public/patient groups. In particular, consultation should take place in relation to the use of data, including acceptability, security and accessibility. This is applicable even where contact with patients is not required as part of the study.
- Evidence to support a CAG application should include details of the engagement of patients in relation to data processing issues carried out to date, the planned patient and public involvement activities that will take place prior to data collection and the continued patient

involvement that will take place throughout the duration of the study and how the results of the research will be fed back to patients. This should include what specific questions have been asked in relation to processing confidential patient data without consent.

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Question A15 - Sample group or cohort

- Please select the main identifying feature(s) of the participants, data or samples being studied. Where research does not involve identification by disease or diagnosis please select the option "Generic Health Relevance".
- Where participants are users of a service, NHS staff or selected from the general public, please include further details in the inclusion and exclusion criteria at A17.
- In the case of healthy volunteer trials, the intended indication for the product under development should be provided.

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Question A16 - First-in-human clinical trials

- This question applies only to Phase 1 clinical trials of investigational medicinal products.
- A First-in-Human clinical trial is a Phase I clinical trial where the product has not previously been administered to humans.
- Applicants should familiarise themselves with the European Medicines Agency's (EMA) guidelines on "Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products" and "Non-clinical studies required before first clinical use of gene therapy medicinal products", which are published on the EMA's website at: <http://www.emea.europa.eu/htms/human/humanguidelines/nonclinical.htm>
- For certain types of clinical trial the MHRA will seek advice from an Expert Advisory Group (EAG) and the Commission on Human Medicine (CHM) before giving authorisation. Examples of trials where expert advice may be sought include First in Human trials with novel compounds:

- where the mode of action involves a target that is connected to multiple signalling pathways (target with pleiotropic effects) e.g. leading to various physiological effects or targets that are ubiquitously expressed
- acting (directly or indirectly) via a cascade system where there may be an amplification effect which might not be sufficiently controlled by a physiological feedback mechanism
- acting (directly or indirectly) via the immune system with a target or mechanism of action which is novel or currently not well characterised
- where there is novelty in the structure of the active substance e.g. a new type of engineered structural format such as those with enhanced receptor interaction as compared with the parent compound
- where the level of expression and biological function of the target receptor may differ between healthy individuals and patients with the relevant disease
- where there is insufficient available knowledge of the structure, tissue distribution, cell specificity, disease specificity, regulation, level of expression and biological function of the human target, including down-stream effects
- acting via a possible or likely species specific mechanism or where animal data are unlikely to be predictive of activity in humans.
- Procedures for EAG/CHM assessment also apply to applications for trials with integrin antagonists targeting leucocyte traffickings except Phase 1 studies in subjects with no previous immunosuppression.
- Detailed guidance on the procedures for seeking advice from EAG/CHM and applying for Clinical Trial Authorisation can be found on the MHRA website at: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=986
- If your application falls into the above categories, please also see the guidance on Question A55.

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Question A18 - Research procedures to be undertaken

- These questions request detailed information about all the interventions and procedures that will be received by participants, or conducted on samples or data.

- The REC will assess the risk and ethical acceptability of what is involved for potential participants. In particular it will wish to consider the nature and number of procedures compared to what a research participant might receive if undergoing treatment or other service provision alone.
- NHS reviewers will use the information to:
 - Assess the cost and resource implications
 - Ensure that necessary practical arrangements are made to support research activities
 - Make necessary risk management arrangements
- In column one give the total number of interventions or procedures, not the additional ones over and above the routine ones.
- Where all or some of the interventions or procedures would be regarded generally as routine care, give the number in the second column.
- In column three give the average time taken to conduct each intervention or procedure. Some activities will overlap but the time for each should still be listed separately, e.g. an in-patient hospitalisation of three days and obtaining a blood sample during the stay lasting 10 minutes.
- In column four give either the name and job title of the individual conducting the research intervention or procedure (if it will always be the same person at all research sites), or give a description of the staff group, e.g. research nurse at site. Please also provide a general description of where the intervention/procedure will take place, e.g. out-patient clinic, GP practice or participant's home.
- Clinical interventions are those that are routinely conducted or requested by a healthcare professional.
- Information given about ionising radiation exposures (e.g. number of diagnostic X-rays, CT scans or courses of radiotherapy) should be consistent with the information provided in Part B Section 3 of IRAS.

Additional guidance for research involving prisoners

- It is expected that the applicant will normally only use questionnaires which have been specifically validated for use with the prison population. If the questionnaires have not been so validated the applicant should provide a clear justification for their use.
- It is recognised that literacy levels among the prison population are very low and the researcher is asked to consider this when selecting questionnaires and any related material.

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Question A19 - Research procedures to be undertaken

- These questions request detailed information about all the interventions and procedures that will be received by participants, or conducted on samples or data.
- The REC will assess the risk and ethical acceptability of what is involved for potential participants. In particular it will wish to consider the nature and number of procedures compared to what a research participant might receive if undergoing treatment or other service provision alone.
- NHS reviewers will use the information to:
 - Assess the cost and resource implications
 - Ensure that necessary practical arrangements are made to support research activities
 - Make necessary risk management arrangements
- Where all or some of the interventions or procedures would be regarded generally as routine care, give the number in the second column.
- In column three give the average time taken to conduct each intervention or procedure. Some activities will overlap but the time for each should still be listed separately, e.g. an in-patient hospitalisation of three days and obtaining a blood sample during the stay lasting 10 minutes.
- In column four give either the name and job title of the individual conducting the research intervention or procedure (if it will always be the same person at all research sites), or give a description of the staff group, e.g. research nurse at site. Please also provide a general description of where the intervention/ procedure will take place, e.g. out-patient clinic, GP practice or participant's home.
- Clinical interventions are those that are routinely conducted or requested by a healthcare professional.
- Information given about ionising radiation exposures (e.g. number of diagnostic X-rays, CT scans or courses of radiotherapy) should be consistent with the information provided in Part B Section 3 of IRAS.

Additional guidance for research involving prisoners

- It is expected that the applicant will normally only use questionnaires which have been specifically validated for use with the prison population. If the questionnaires have not been so validated the applicant should provide a clear justification for their use.

- It is recognised that literacy levels among the prison population are very low and the researcher is asked to consider this when selecting questionnaires and any related material.

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Question A20 - Withdrawal of treatment or other services normally provided.

- Sometimes a research protocol requires withdrawal of existing treatment or service provision. It may for example be justified to stop current therapy during a "washout period". Reviewers will be concerned to ensure that treatment is withdrawn only when absolutely necessary. You should explain the possible consequences of withdrawing treatment and how you would minimise the possibility of any harm.
- The participant information sheet should explain where treatment is being withheld, making absolutely clear what is involved, including the likely level of discomfort and risk, procedures to minimise the risks and whether extra assessments will be involved.

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Question A21 - Duration of study for each participant

- Duration of participation should be calculated from when participants give informed consent until their last contact with the research team.

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Question A22 - Potential risks and burdens

- Your answer should identify potential risks and burdens (see table below) but it should be more than a comparative list. You should weigh up the risks in relation to the benefits, exploring the likelihood of both and the consequences of potential harm. It helps to put yourself in the participants' shoes and try to imagine how he or she would see the project. If it is possible, discuss with potential participants. This is another area where consultation with patients or members of the public may provide support. It is helpful to show evidence to the REC that patients, carers, service users or members of the public with relevant experience think the risks and burdens, including the practical arrangements, are likely to be acceptable to participants. You may find it helpful to involve the patients, carers, service users or members of the public that you worked with in completing this question.

- Include any potential for distress, discomfort and/or inconvenience which might be experienced by a research participant, with an explanation of why it is necessary and what has been done to minimise the effects. Most research has potential to cause some distress even if this is felt to be minimal, e.g. breach of confidentiality, upsetting participants in interviews.
- Where the research only involves the use of data, consideration should still be given to the risks for patients associated with any breach of confidence or failure to maintain data security.
- Potential risks and burdens should be described in the participant information sheet in such a way that potential participants can clearly understand what is involved if they consent to take part.
- Research sponsors should have in place systems to monitor and respond to developments as the research proceeds, particularly those which put the safety of individuals at risk, and to ensure the design and conduct of the research is modified accordingly.
- It is not acceptable to state "not applicable" in answer to this question.
- Balance of risks and benefits of participation in, or exclusion, from research

	<i>Risk</i>	<i>Benefit</i>
Inclusion	<ul style="list-style-type: none"> ◊ Risk of research procedures or withholding standard procedure ◊ Risk of new therapy ◊ Intrusion ◊ Risk of breach of confidentiality ◊ Change of relationship with healthcare professional ◊ Possible misunderstanding (especially for those who have difficulty with English) 	<ul style="list-style-type: none"> ◊ Better supervision ◊ More visits ◊ Evidence that results of treatment may be better within a trial
Intrusion	<ul style="list-style-type: none"> ◊ Belonging to an under-researched group (e.g. children or women) ◊ Dangerous therapy 	<ul style="list-style-type: none"> ◊ No risk/burden of research procedures ◊ No potentially

- | | |
|--|--|
| ◊ Ineffective therapy | inferior new therapy |
| ◊ Incorrect dosages | ◊ No intrusion |
| ◊ Stagnant or inappropriate healthcare | ◊ No risk to confidentiality |
| | ◊ No change of relationship with healthcare professional |

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Question A23 - Disclosure of information from interview/questionnaire

- If interviews touch on sensitive areas, reviewers will consider the experience of researchers and how they will handle these aspects.
- Where the research might lead to unexpected disclosure of information by participants that could require notification or other follow-up action by the researcher, please describe how this would be handled.
- Reviewers will wish to be assured that appropriate arrangements are in place including support for the researcher.
- The participant information sheet should make it clear under what circumstances action may be taken by the researcher.

Additional guidance for research involving prisoners

- Applicants should consider how they will deal with potential disclosure of information required by Prison Rules, i.e. any intention on the part of the participant or another prisoner to self-harm, harm another named person or pose a threat to security. Careful consideration should also be given to the policy for disclosure of any other sensitive information which might come to light during the research, e.g. misuse of drugs or other breaches of Prison Rules.

The information sheet should state clearly what information would be disclosed by the researcher.

- The REC would expect the applicant to provide participants with access to an appropriately trained person should they become upset, agitated, angry, etc during any interviews/group discussions/completion of questionnaires. The applicant should be aware in this context of the general levels of mental health of the prison population.

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Question A24 - Benefits to the research participant

- You should state here any potential benefits to be gained by the research participant through taking part in the research either now or in future. However, don't over-emphasise the benefits. In some cases there may be no apparent benefit.
- Some studies purport to show a benefit to taking part in any therapeutic trial but a recent meta-analysis could not support this and demonstrated significant methodological problems in previous work. It seems that the majority of those who participate find it a positive experience, but it is probably best to refrain from claiming any therapeutic benefit simply from being in the trial.
- There is clearer evidence that patients and service users experience benefit from taking part in observational research.

Additional guidance for research involving prisoners

- The applicant must ensure that the participants clearly understand that by participating in the study their care, life in prison or parole will not be affected in any way.

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Question A25 - Arrangements at the end of the trial

- Describe the arrangements the sponsor is making, if any, for continued access by the participant to any benefits or intervention, which he or she may have obtained during the research.
- There is no legal or policy requirement to provide continued treatment to participants once they have completed the trial. It is an issue to be considered on a trial by trial basis. However, the sponsor's plans must be made clear to potential participants before consent is

sought. Where a commitment is made to provide continued treatment, review bodies will seek assurance that agreement has been reached on funding responsibilities.

- Researchers should consider the following options:
 1. No treatment available after the trial.
 2. Treatment available to all those in the trial already taking it.
 3. Treatment available to all participants.
 4. Treatment available to patients on a named patient basis.
 5. Drug available on an open label basis for a cohort observational study.

- Reviewers will wish to consider the following issues:
 - Will the subjects understand the arrangements at the end of the trial prior to agreeing to participate?
 - Who, if anyone, is in a position to provide treatment after the trial?
 - What are the resource and financial implications of providing continued treatment? Would these jeopardise the trial?
 - Who would carry the liability for provision of treatment outside the trial?
 - How soon will the results be available for use after the conclusion of the trial?
 - Will the results of the trial provide unequivocal evidence of efficacy?

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Question A26 - Potential risks to the researchers

- The research sponsor should consider the safety and well-being of researchers. For example, there may be risks for lone researchers visiting participants at home. Describe the measures proposed to address such issues.

Additional guidance for research involving prisoners

- You should ensure that the safety of the researcher has been considered and that the researchers have the relevant experience to be able to assess and to deal with possible risks.

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Question A27-1 - Identifying potential participants

- Where potential participants will be referred to a separate research team, the arrangements for identification and referral must be clearly described here. Details of the centres undertaking such referral of NHS patients must be given in Part C of IRAS. Where potential participants are referred as NHS patients to a separate research team outside the NHS, any publicity, letter of invitation and/ or written information for participants must explain this arrangement clearly.

Additional guidance for research involving prisoners

- Justification is required if prison staff are being used to select or approach suitable participants as this could well bias the results of the study. It is generally unacceptable for prison staff to be used as gatekeepers.

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Question A27-2 - Screening of identifiable personal information

- Please give details of the sources of identifiable personal information that will be used to identify potential participants.
- Normally only a member of the patient's existing clinical care team should have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients. If the research proposes to use someone outside the clinical team to identify suitable participants, or as first contact with the participant, the reason for this should be explained.
- Where patient or disease registers are used to identify potential participants give brief details of the consent and confidentiality arrangements of the register.

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Question A27-3 - Screening of identifiable personal information

- Please give details of the sources of identifiable personal information that will be used to identify potential participants.

- Normally only a member of the patient's existing clinical care team should have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients. If the research proposes to use someone outside the clinical team to identify suitable participants, or as first contact with the participant, the reason for this should be explained.
- Where patient or disease registers are used to identify potential participants give brief details of the consent and confidentiality arrangements of the register.
- Under the General Data Protection Regulations (GDPR), in most cases you will need to provide participants with transparency information about your legal basis and other details of processing personal data from 25 May 2018. Please refer to the [Health Research Authority \(HRA\) website](#) for further information.

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Question A27-4 - Access to personal data outside the care team

- Normally only a member of the patient's direct healthcare team should have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients. If the research proposes to use someone outside the clinical team to identify suitable participants, or as first contact with the participant, the reason for this should be explained.
- The "direct healthcare team" are clinicians directly responsible for providing routine care and treatment to individual patients together with their administrative support staff. Normally such clinical staff will have direct contact with the patients. However, as pathology staff also directly support the care provided to patients they would also be included within the boundaries of the healthcare care team. Social Workers are not usually part of the healthcare team and disclosures of confidential information to social services staff should be undertaken with explicit patient consent, at least initially, in order to provide a basis for further disclosures based on implied consent.

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Question A27-5 - Consent to access identifiable data

- Consent for secondary uses of identifiable data such as health research must be explicit. Implied consent is only acceptable where there is a basis for implying consent such as where the patient agrees to be referred to another service. Although custom and practice has been that researchers have often been given access to records in order to identify relevant patients in order either to extract relevant data or to invite those patients to seek consent, this involves a breach of confidentiality. Consent should be sought by the clinical care team therefore to allow researchers access to the records in order to extract information or to identify patients with a view to informing them about a research study, where clinicians or their staff are unable to do this themselves. (See guidance on the Confidentiality Advisory Group (CAG; please refer to the Health Research Authority (HRA) website for more information about CAG (<http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/>); applying to CAG (<http://www.hra.nhs.uk/research-community/applying-for-approvals/confidentiality-advisory-group-cag/>) ; a n d C A G r e s o u r c e s (<http://www.hra.nhs.uk/resources/confidentiality-advisory-group/>))
- If you plan to access identifiable data without prior consent you should ensure that you have selected the option to apply to CAG (see question {QNumber(Q_A_4)} of the IRAS Project Filter).

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Question A28 - Advertisements

- All advertising material designed to recruit participants must be reviewed by the REC. This includes posters, television and radio broadcasts, videos, CDs and web pages. Copies of these (printed material, audio or video tapes, transcripts etc) should be included with your application and give a version number and date.
- Recruitment material should be restrained in tone. Care should be taken not to over-emphasise potential benefits or make other inducements.
- You should state who would be the first contact point for anyone answering an advertisement, and give brief details of their professional background and training for this task.

Additional guidance for research involving prisoners

- Recruitment material needs to take into account the general literacy levels of the prison population, and applicants should consider how they will recruit non-literate participants. Participants should clearly understand from any advertising material that their participation is entirely voluntary and that they can decide not to participate or withdraw from the study at any time without their parole, care or life in prison being affected in any way.

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Question A29 - Approaching participants

- Please explain how participants will be approached and who will be involved.
- Participation in a research project must be entirely voluntary, and no one must be coerced to participate in a research project against his/her will. Researchers should avoid exerting undue influence when approaching potential participants. No sanctions should follow if the participant decides to leave the research at any time.
- The initial approach to potential participants should normally be made by a member of the healthcare team. If researchers other than members of the healthcare team propose to approach potential participants directly, the reason for this approach should be explained.
- Copies of documentation used to approach potential participants should be enclosed with all applications (e.g. letters to clinicians or other health professionals, letters from clinician to patient).

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Question A30-1 - Informed consent

- Informed consent and participant information sheet guidance is provided at: <http://www.hra-decisiontools.org.uk/consent/index.html/> . This guidance:
 - Covers consent in adults, children, young people and adults not able to consent for themselves (in both emergency and non-emergency situations) and takes into account UK-wide requirements.
 - Provides some examples and suggested text, which should be considered as a framework, not a rigid template: we would encourage you to think carefully about how best to inform potential participants. One size does not fit all: you do not need to produce the same participant information sheet (PIS) and consent form to support consent for a questionnaire study as you would to recruit into a drug trial.
 - Highlights that the best way to make sure your consent documentation is fit for purpose is to test it with patient groups or members of the public with relevant experiences.
- Where you have worked with or sought advice from patients, carers, service users or members of the public you should explain how what they did or what they said helped to produce or shape the PIS, consent form, and any other participant-facing information. It will be helpful to show the REC the details of how this has been done. You may find it helpful to

involve the patients, carers, users or members of the public you worked with in completing this question.

Legal and ethical requirement for informed consent

- For most types of research, it is both a legal and ethical requirement to obtain informed consent from participants able to consent for themselves. (For guidance on research involving *adults unable to consent for themselves (including research involving emergency treatment)* and *children*, please refer to the question-specific guidance on Part B Sections 6 and 7 respectively.)
- It is not expected that research will use consent as a legal basis for processing personal data under the General Data Protection Regulations (GDPR). Please refer to the [Health Research Authority \(HRA\) website](#) for further information
- There are exceptions in which it is not a legal requirement to obtain informed consent, for example where the research is limited to use of the following:
 - Data that has been anonymised and is no longer personal data within the meaning of the Data Protection Act or pseudonymised. For further information please see the [Information Commissioners Office \(ICO\) guidance document - *Anonymisation: managing data protection risk code of practice*](#).
 - Personal data where an application has been given approval by the Health Research Authority (HRA) following an application to the Confidentiality Advisory Group (CAG), for processing of the data without consent under Section 251 of the Health and Social Care Act 2001. See <https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/confidentiality-advisory-group/> for further guidance.
 - "Existing holdings" of tissue under the Human Tissue Act 2004, i.e. "relevant material" which was already held prior to 1 September 2006.
 - Tissue from the living, which is not identifiable by the researcher and where the research is ethically approved by a NHS REC under section 1(9) of the Human Tissue Act.
- If you propose not to seek consent, please explain why in your answer to this question. Where consent is not a legal requirement, you should still consider whether it would be feasible and ethically justified to seek consent. Research evidence indicates that the public value their right to choose whether or not to participate in research, even where a study has been approved by a REC.

Arrangements for seeking consent

- For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. A capable person will:

- Understand the purpose and nature of the research.
 - Understand what the research involves, its benefits (or lack of benefits), risks and burdens.
 - Understand the alternatives to taking part.
 - Be able to retain the information long enough to make an effective decision.
 - Be able to make a free choice.
 - Be capable of making *this particular decision* at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).
- Exclusive reliance on handing out the participant information sheet should be avoided. Researchers should be able to explain the study clearly to potential participants. Reviewers will consider what training and experience the researchers have had in seeking consent. RECs will seek reassurance that researchers understand the ethical principles underpinning informed consent and are able to assess capacity.
 - Where the research team will be recruiting participants whose capacity is likely to be borderline or to fluctuate, please say how capacity will be assessed and by whom, and what relevant knowledge and/or expertise this person will have. Where adults unable to consent for themselves are to be included, separate information about recruitment should be provided in Part B Section 6 – detailed guidance is available in this section.

Participant information sheets

- Advice on writing the participant information sheet and templates can be found at <http://www.hra-decisiontools.org.uk/consent/>. Reviewers will generally expect applicants to follow these guidelines. They should be regarded as setting out the basic minimum information, which can be supplemented if required.
- Information should explain the study clearly, and the language used should be suitable for a lay person. All technical words must be explained. The tone of the information sheet should be invitational and not coercive.
- The REC expects a copy of the participant information sheet to be given to the research participant to be kept for reference.
- Where the schedule of study procedures is complex, it is recommended that a flow chart or table should be prepared for participants and included with the application.

Vulnerable participants

- Consent must always be voluntary. Where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected.
- Particular consideration should be given to informed consent arrangements where participants are in a dependent relationship with the research team. Examples include:
 - Students participating in research by their tutors.
 - Members of staff participating in research carried out, or formally supported by, the management of their organisation.
 - Residents of care homes.
- In such cases, participants may feel under an onus to participate. It is important that every effort is made to avoid coercion and ensure consent is voluntary. Your answer to this question should say what steps will be taken.

Additional guidance for research involving prisoners

- The participant information sheet should include specific guidance for prisoners on the following:
 - the obligation on the researcher to disclose any intention on the part of the participant or another prisoner to commit self-harm, harm a named person or pose a threat to security, if this comes to light during the research
 - any other information the researcher plans to disclose if it comes to light during the research
 - that participation will not affect their parole, care or life in prison in any way.
- When drafting the information sheet the researcher should bear in mind that the average reading age of prisoners is lower than that in the general population.

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Question A30-2 - Recording consent in writing

- The consent to take part in a study should be recorded in a patient's notes and in the study records.
- Please enclose a copy of the proposed consent form when submitting your application. Advice on the consent form and templates can be found on the Health Research Authority (HRA) web site at <http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/> .
- If you do propose not to obtain consent in writing, you should justify this. The REC usually requires that written consent be obtained for all but the most minor procedures. In studies involving postal questionnaires where the burdens are insignificant and sensitive topics are not involved, the REC will normally regard the return of the questionnaire as adequate evidence of consent. This is sometimes called "implicit consent".
- Where a participant is unable to sign or mark a document to indicate their consent, arrangements should be made for their consent to be witnessed and this should be documented.

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Question A30-3 - Justification for not seeking consent to process identifiable data

- This question applies only to applications to the Confidentiality Advisory Group (CAG) to process identifiable patient data without consent.
- Explain why it is not practicable for either your organisation or the current holder(s) of the information you require to obtain consent from patients to use their information. Robust arguments are sought here. For example, the data may be very historical and people would be difficult to trace and/or deceased.
- Please see the principles document provided on the Health Research Authority (HRA) website (at: <http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/>) for details of CAG considerations when providing advice to HRA.
- Section 251 support should not be used where consent is possible through the procedures outlined in the Mental Capacity Act 2005 and should not be used to override explicit dissent. Where Section 251 support is given then for the purposes of the MCA, the research is no longer regarded as “intrusive” and so would be exempt from the requirements of Sections 31-33, other than as stipulated as a requirement of approval.
- The Mental Capacity Act Code of Practice 2005, which provides practical guidance for the implementation of the Mental Capacity Act 2005, describes how and when consent can be

obtained of a person has been confirmed as not capable of giving consent for themselves. This is available at <https://www.gov.uk/government/publications/mental-capacity-act-code-of-practice>. Please consult this document before applying. Section 11 has the relevant information for researchers.

- As a general principle, the process of seeking consent should be undertaken by the original holder of the data. CAG occasionally recommends approval for a research body to act as data processor for the Trust(s) responsible for the data and to write to patients direct in order to seek consent but the letter should appear to come from the relevant Trust / GP practice.

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Question A31 - Time allowed to decide to take part

- Potential participants need time to consider fully the implications of taking part in research. They should be able to ask questions and reflect. Participants should not be rushed into decisions.
- There are no fixed guidelines for the time to be allowed to participants. It has been common practice to suggest a minimum of 24 hours, but this is not an absolute rule. Each study should be considered on its own merits. If you feel that a shorter period is reasonable in the circumstances and taking into account the nature of the study, please justify this in your answer.

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Question A32 - Multiple participation

- Particular care must be taken to ensure that participation in multiple studies will not compromise patient safety or undermine the scientific basis of the study. The REC may also wish to consider the overall burden on participants.

Medicinal trials

- It is important to distinguish medicinal trials (CTIMPs) from other studies. For CTIMPs, the guidance from the Association of the British Pharmaceutical Industry (ABPI) is that there should be a gap of 4 months between trials. The US Food and Drug Administration (FDA) stipulate 28 days. The investigator should also consider whether there are reasons for extending this period.

- For Phase 1 CTIMPs, investigators should use a process such as The Over-Volunteering Prevention System (TOPS) to identify any volunteers who are putting themselves at risk by participating on more than one trial. Further information about TOPS is available at www.tops.org.uk.

Other research

- For studies other than CTIMPs, there are no established guidelines. Multiple participation is an ethical issue for the REC to consider as part of its review. There is little published literature on this issue, but what there is suggests that the public are willing to take part in more than one study. However, you should think about the following:
 - The burden of participation in more than one study and the psychological impact.
 - Any possible impact on the results of each study.
 - The consequences for the design and scientific validity of your study.
 - Recovery periods.
- The decision should be the patient's provided that there are no overriding safety or design considerations.

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Question A33-1 - Research participants who may have difficulties in adequate understanding of English

- The inclusion or exclusion of potential participants who may have difficulties in adequately understanding written or verbal information in English raises ethical issues.
- If they are to be included, you should explain what measures will be taken to provide necessary translation of written information and interpretation. In a multi-site study, the CI is responsible for ensuring that Principal Investigators and collaborators will make the necessary arrangements at each research site. There are strong arguments in terms of cost and consistency for translation of the documents to be commissioned centrally and then made available to each site as necessary.
- Any proposal to exclude such participants should be clearly justified in the application.
- The acceptability of the *plan to implement* these arrangements in a particular locality falls within the scope of site-specific assessment by the NHS R&D office or the local REC for the site.

- If you have concerns about how these issues relate to your research you should seek specific guidance from the REC in your application.

Recruitment of participants in Wales

- If you are recruiting patients for a trial in Welsh centres you should note that provision of information for patients is governed by the Welsh Language Act (1993). The Act established the principle that in the conduct of public business and administration of justice in Wales, the English and Welsh languages should be treated on the basis of equality. This principle of equality offers the public the right to choose which language to use in their dealings with public organisations (including the National Health Service) and recognises that members of the public can express their views and needs better in their preferred language. In research, this presents particular ethical issues relating to informed consent.
- There is considerable geographical variation in the use of the Welsh language within Wales. Before submitting your application it is recommended that you seek advice from local NHS R&D office(s) about the language requirements of the local population and the Welsh language policies in place at the site.
- Please indicate in your answer to this question whose advice you have sought on this issue, as this will provide assurance to the main REC that the local issues have been appropriately addressed. This will be especially helpful where the main REC is in another UK country. The main REC may seek its own advice from local RECs for the research sites if necessary.
- If Welsh translations of patient information and consent forms are required, a list of translators can be obtained from the Welsh Language Board (0129 20 224744).

Additional guidance for research involving prisoners

- Certain prisons have a large population of non-English speaking prisoners and the applicant is asked ensure that the information sheets are translated into the relevant languages or to provide interpreters. Excluding those prisoners who have the most problems with understanding English might well exclude those with the most significant physical and mental health needs and thus bias the results of the study.

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Question A34 - Providing information during the study

- Participants should be aware of any new information that emerges during the research, which might affect their participation. You should describe your strategy for looking for, and disseminating, such information.

Question A35 - Loss of capacity to consent

The following guidance applies to all research except for clinical trials of investigational medicinal products (CTIMPs) - (Issues relating to consent in CTIMPs are governed by Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004.)

For other research:

- **Consent under common law cannot generally be said to endure the loss of capacity to consent by a participant.**
- **It is therefore necessary for researchers to consider what steps they would take in the event of a participant losing capacity to consent during the project.**
- **You should tick the most appropriate option in A35 and give brief details of the action that would be taken, particularly in relation to tissue samples or data already collected.**
- **Researchers are not obliged to monitor the capacity of participants proactively during the study - However, they should be ready to address the consequences of a loss of capacity should this come to their attention at any point.**

Option 1 – Withdrawal of participant and anonymisation of tissue/data

- **The participant would be withdrawn from the study - No further clinical or non-clinical interventions or procedures would be carried out on the participant under the study protocol - No new samples or personal data would be collected.**
- **Subject to ethical approval, tissue samples or data already collected in relation to the participant may be retained and used for the purposes for which consent has already been given, provided they are effectively anonymised and no longer identifiable to the research team or any other persons to whom access will be given - Further data may be collected provided that it is received in anonymised form and is not identifiable; consent for this is not a legal requirement.**
- **Alternatively, samples and data may be disposed of.**

Option 2 – Withdrawal of participant, retention of identifiable tissue/data

- **Subject to ethical approval, tissue samples and data already collected may be retained in identifiable form and used in the research provided that properly informed and expressed consent for this was given prior to the onset of incapacity.**
- **If you select this option, you should cover the issue explicitly in the participant information sheet - Participants should be aware that in the (perhaps unlikely) event**

of a loss of capacity, the research team would retain tissue and personal data collected and continue to use it confidentially in connection with the purposes for which consent is being sought - This could include further research after the current project has ended provided that this is made clear in the information for participants.

- The researcher may then continue to rely on such consent following loss of capacity.
- Approval will not be required under either the Mental Capacity Act 2005 (in England and Wales) or the Adults with Incapacity (Scotland) Act 2000.

Option 3 – Participant remains in the research study

- Under this option, the participant would remain in the research study and may undergo further interventions and procedures, including collection of new samples and personal data, as required by the protocol.
- This would constitute "intrusive research" for the purposes of the Mental Capacity Act 2005 in England and Wales and would require approval under section 30 of the Act - In Scotland, approval would be required under section 51 of the Adults with Incapacity (Scotland) Act 2000 - In Northern Ireland, the common law requirements would apply.
- *If you select this option, you should complete the detailed questions in Part B Section 6 of the application form* - Note that these questions would apply only to the situation following loss of capacity, not to the initial inclusion of participants with consent - Your answers in Part B Section 6 should justify the proposal to undertake *further research* following loss of capacity and give information about the procedures you would follow if this occurred.
- This option may apply where research participants are suffering from an impairing condition and their capacity to consent is borderline or fluctuating - Participants could be initially recruited with consent but lose capacity during the research - It may be reasonable to continue to include them in the research, subject to appropriate safeguards, to achieve the research objectives and realise the benefits either to participants themselves and/or to science and society.
- Continued research on participants following loss of capacity would only be approved by the REC if the research met in full the criteria for including such participants in research, i.e. the nature of the research is such that it would have been justified to include participants lacking capacity from the outset.

Option 4 – Not applicable as informed consent will not be sought from any participants

- In some cases, the issues around loss of capacity will not arise at all because it is not proposed to seek informed consent from any participants in the study.
- This could apply in the following cases:

- **Research using tissue samples where consent is not a legal requirement under the Human Tissue Act or the Human Tissue (Scotland) Act.**
- **Research using data where no identifiable data will be processed by researchers outside the clinical team.**
- **Research involving the processing of identifiable patient data without consent with Section 251 support from the Health Research Authority (HRA).**
- **You may also select "not applicable" where the research only involves children without capacity and will rely in all cases on informed consent from a person with parental responsibility - However, if informed consent is to be obtained from children considered capable of giving consent for themselves under the Gillick principles, consideration should be given to the implications of loss of capacity during the study and one of the other options should be selected.**

Further guidance

- [Office of the Public Guardian - Mental Capacity Act Code of Practice.](#)

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Question A36 - Data processing activities

Under the General Data Protection Regulation (GDPR), there is a strong emphasis on implementing safeguards for personal data for research. Safeguards are the measures that are taken to ensure that data is processed securely, accurately and in accordance with data protection principles. Please refer to the [Health Research Authority \(HRA\) website](#) for further guidance.

<i>Activity</i>	<i>Guidance</i>
Access to medical records by those outside the direct healthcare team	This should only be undertaken with consent or Section 251 approval.
Electronic transfer of	Where personal data is transferred electronically, data should be encrypted during transfer.

d a t a b y
magnetic or
optical
media, email
or computer
networks

Sharing of data with other organisations Except where such disclosure has consent or approval under Section 251, only anonymised data should be shared. Where data has been effectively pseudonymised it should only be shared on the basis that the recipient cannot disclose pseudonymised data to third parties and is not permitted to link the data with other data which might render the information more identifiable.

Export of data outside the EEA For guidance about transfer of data outside of the European Economic Area (EEA) please refer to the [Health Research Authority \(HRA\) website](#).

Use of personal addresses, postcodes, faxes, emails or telephone numbers It should be remembered that such personal contact details can be sensitive information, either because individuals are concerned about identity theft or because of domestic violence etc.

Publication of direct quotations from respondents Should be anonymised

Publication of data that might allow identification of individuals In general, publication of case histories should be effectively anonymised. Where identification is possible it is essential that this is only undertaken with consent.

Storage of personal data on manual files (including X-rays) Paper and other manual files should be appropriately filed and stored securely.

Storage on NHS computers Appropriate access controls need to be in place to ensure that access to confidential research information is restricted to those who need access.

Storage on home or participants" or research Under no circumstances should patients" or research participants" personal data be stored on a home or other

other personal computer.
personal computers

Storage on university computers Appropriate access controls need to be in place to ensure that access to confidential research information is restricted to those who need access.

Storage on private company computers Appropriate access controls need to be in place to ensure that access to confidential research information is restricted to those who need access.

Storage on laptop computers Use of laptops and other portable devices is to be avoided. Where it is necessary for them to be used, data must be encrypted and the data uploaded onto a secure server or desktop as soon as possible and the data removed from the portable device as soon as possible and using appropriate data destruction software.

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Question A37 - Physical security of data storage

- Under the General Data Protection Regulation (GDPR), there is a strong emphasis on implementing safeguards for personal data for research. Safeguards are the measures that are taken to ensure that data is processed securely, accurately and in accordance with data protection principles. Please refer to the [Health Research Authority \(HRA\) website](#) for further guidance.
- Please describe where all personal data of participants will be stored. Explain if filing cabinets, cupboards and/ or rooms will be locked and who has access. Give details of security arrangements for personal data held on computer, especially where laptop computers are used.
- Information about security arrangements should *not* be detailed enough to enable access by anyone viewing this application.

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Question A38 - Confidentiality of data

- Under the General Data Protection Regulation (GDPR), there is a strong emphasis on implementing safeguards for personal data for research. Safeguards are the measures that are taken to ensure that data is processed securely, accurately and in accordance with data protection principles. Please refer to the [Health Research Authority \(HRA\) website](#) for further guidance.
- Please give details of the overall arrangements to respect confidentiality of personal data and meet the requirements of the Data Protection Act. Give details of policies or guidance that will be followed, e.g. NHS Code of Confidentiality.
- For Confidentiality Advisory Group (CAG) applications, it is a requirement that those individuals accessing identifiable patient data should owe an equivalent duty of confidentiality to a health professional. Please provide details of confidentiality policies, confidentiality clauses in staff contracts and measures to ensure that all staff are aware of and work to appropriate confidentiality standards.

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Question A39 - Separation of identifiers from clinical data

- This question applies only to applications to the Confidentiality Advisory Group (CAG) to process identifiable patient data without consent.

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Question A40 - Access to personal data during the study

Access to data for monitoring and audit

- Monitors and auditors from pharmaceutical companies, trial centres and NHS R&D offices, and regulatory inspectors may require access to patients' clinical notes to verify or cross check data. Review bodies are likely to accept protocols that incorporate such arrangements provided that the following guidelines are observed:
 - Participants are told in the information sheet who may have access to their medical records and trial data, and why.
 - Such individuals must have an appropriate professional background. If there is concern regarding the appropriateness of a person this should be checked with the REC.
 - Participants have signed a consent form to state they have read the participant information sheet and understood the information it contains.
 - In some circumstances it may be appropriate to add that the data in an anonymous form may be used for preparation of the trial report, and for submission to Government agencies as part of the procedures for marketing any new medicine.

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Question A41 - Analysis of data and location

- Explain where the data will be analysed and the arrangements for ensuring confidentiality of personal data during transfer of data. Give details of any plans to export data outside the UK.
- For guidance about transfer of data outside of the European Economic Area (EEA) please refer to the [Health Research Authority \(HRA\) website](#).

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Question A42 - Data custodian

- This question is asking for details of the individual specifically responsible for the data for this

study as well as the Data Controller organisation.

- Give details of who will be responsible for the use, security and management of all data generated by the study.

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Question A43 - Retention of identifiable data

- Please note this question only relates to retention of personal data.
- Where valid consent is in place, identifiable data may be retained, but consideration should be given at the end of the study to whether it is possible to reduce the identifiability of data retained following record linkage and validation.
- Where data is to be processed without consent using Section 251 support (please refer to: <https://www.hra.nhs.uk/about-us/committees-and-services/confidentiality-advisory-group/>), there is a requirement to reduce the identifiability of the data at the earliest reasonable point and to anonymise/pseudonymise the data effectively at the end of the study. Describe how identifiable patient data will be destroyed once work is complete. You should not include details of any data destruction software to be employed here but include it instead in Part B Section 9 of IRAS.

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Question A44 - Data storage

- Please indicate in your answer to A45 whether the proposed retention period and storage arrangements are subject to any policy or guidance from the research host or your employer. Explain how and when data will be destroyed.

Audio/video recording and the observation of patients

- Informed consent should be obtained from the research participant(s) involved. The participant information sheet should specify the uses to which the material might be put, how the material will be stored and how and when it will be destroyed. It should be noted that videos should not be used for commercial purposes.

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Question A45 - Data storage

- Please indicate in your answer to A45 whether the proposed retention period and storage arrangements are subject to any policy or guidance from the research host or your employer. Explain how and when data will be destroyed.

Audio/video recording and the observation of patients

- Informed consent should be obtained from the research participant(s) involved. The participant information sheet should specify the uses to which the material might be put, how the material will be stored and how and when it will be destroyed. It should be noted that videos should not be used for commercial purposes.

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Question A46 - Payment to research participants

Payments and benefits

- Payment of participants should be ethically justified. The REC will wish to be reassured that research participants are not being paid for taking risks or that payments are set at a level which would unduly influence participants.
- Information on any payments or benefits must be included in the participant information sheet.
- If proposing payments, you should consider the possibility of non-cash payments, particularly for children (e.g. book tokens).
- If you decide to introduce payments after receiving a favourable opinion from the main REC, these must be notified to the REC as a substantial amendment and ethically reviewed before being implemented.

Reimbursement of expenses

- Research participants should not be substantially out of pocket as a result of taking part in a research study.
- Payment in cash or kind to participants must only be for costs such as travel expenses, child-care expenses, meals and demonstrable loss of earnings etc.
- Consideration should be given to any expense involved in returning postal questionnaires.
- If it is not possible to reimburse such expenses this should be explained before the research participant is recruited. A clear statement should be included in the participant information sheet setting out the position on reimbursement.

Payment models

	<i>Market Model</i>	<i>Wage Payment Model</i>	<i>Reimbursement Model</i>
Justification	Recruitment of participants is vital to research and the monetary incentive will facilitate this.	Participation in research takes time and effort and may include uncomfortable procedures.	There should not be any financial sacrifice by the research participant.
Function	Incentive	Compensation for time and effort	Reimbursement of expenses

Requirements of ICH GCP (applies to medicinal trials)

3.1.2 The IRB/IEC should obtain... information about payments and compensation available to subjects.

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence to trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: the anticipated, prorated payment, if any, to the subject for participating in the trial.

Additional guidance for research involving prisoners

- Applicants who are considering offering a payment to participants should seek the advice of the prison governor on its suitability. Payment includes vouchers or gifts as well as actual cash.

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Questions A47 - Payment to researchers

- This question is concerned with "in pocket" financial payments or additional benefits to be provided direct to researchers personally, over and above the costs of conducting the research. Such payments could include, for example, contributions to a library, additional equipment not actually required for the research, social events etc. The question is not concerned with payments agreed between the sponsor and NHS care organisations or other sites to reimburse the costs of hosting the research.
- Personal payments or benefits to researchers should not be set at a level to cause undue influence.
- You should record the fact that researchers are receiving personal payments or benefits in the participant information sheet. See the guidance on informed consent on the Health Research Authority (HRA) website at: <http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/>

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Question A48 - Conflicts of interest

- Information should be given about any potential conflict of interest for the Chief Investigator or any other investigator or key collaborator in undertaking the proposed research.

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Question A49-1 - General Practitioner

- In the case of any clinical research, the participant's GP (or other health care professional responsible for the care of the participant) should be informed that his/her patient has agreed to take part. It is the Chief Investigator's responsibility to ensure that the necessary arrangements are made.
- A copy of the proposed information sheet or letter to the GP/health professional must be submitted with all applications.
- It is important to ensure that the health of the research participants at the time of recruitment and during the study is appropriate to the demands made by the research. Special care must be taken to advise the GP/health professional of any aspects of the project that will affect day-to-day treatment given by them. In particular they should be informed about any trial medication, making clear any side effects and potential interactions with other drugs.
- In the case of non-clinical research, it is a matter of judgement whether GPs or other health professionals should be informed. Applicants should consider whether study participation could have implications for care by other professionals or it is possible that participants could approach them for advice about any aspect of the study. If so, it may be helpful for the GP/health professional to be aware of their patient's involvement. Advice on this may be sought from the REC.

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Question A49-2 - Permission to notify the GP

- The research participant should be advised in the participant information sheet that his/her GP/health professional will be approached.
- Normally the REC would expect that any research participant who refused permission to approach their GP should be excluded from the project. If you propose an exception to this requirement (e.g. in a GUM clinic) you must fully justify this to the REC making clear any special arrangements.

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Question A50 - Study registration

All applications should include information in the free text box. The free text box should either provide information about registration or the justification for not registering the research. Where the research is registered, please include reference numbers in A5-1.

Policy and guidance

- The Declaration of Helsinki of the World Medical Association (revised 18 October 2008 at Seoul) states:

"19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."

- The World Health Organisation (WHO) regards trial registration as the publication of an internationally agreed standard dataset about a clinical trial on a publicly accessible database managed by a registry conforming to WHO standards. The standard dataset is published by the WHO International Clinical Trials Registry Platform (ICTRP) at <http://www.who.int/ictip/network/trds/en/index.html>.
- It is government policy in the UK to promote registration of clinical studies and public access to research findings affecting health and social care. For more information see <http://www.dh.gov.uk/en/Researchanddevelopment/A-Z/Researchgovernance/index.htm>

Options for registration

- The International Standard Randomised Controlled Trial Number (ISRCTN) is a simple numeric system for the identification of clinical trials worldwide. The ISRCTN Register accepts the registration of randomised controlled trials and any other research study designed to assess the efficacy of health interventions in a human population. This includes both observational and interventional studies. The Register provides a unique number that can be used to track each trial throughout its lifecycle from initial protocol to publication of results. For more details go to: <http://www.isrctn.com/>
- Alternatively, clinical research may be registered at <http://www.clinicaltrials.gov> (a register of studies in the United States and around the world) or through the metaRegister of controlled trials at http://www.controlled-trials.com/mrct/mrct_about
- For other types of research, registration is also encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists.
- Further guidance will be added on options for registering non-clinical studies in due course.
- In general, registration is not expected for projects undertaken entirely for educational purposes below doctoral level.

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Question A51 - Dissemination of results and publication

- The results of research should be reported, whether through publication in peer reviewed journals or other means of dissemination. Negative as well as positive results should be published, or at least made publicly available.
- Consideration should be given to providing feedback on the results to research participants, interested groups and communities (see Question {QNumber(Q_A_53)}).
- It is important that the results of the study are made available, and see a role for the public in helping to do this well in a way which is accessible to multiple audiences. Where you have worked with patients, patient groups, carers, service users or members of the public you should explain how their involvement or advice will support the feedback and dissemination of study results. You may find it helpful to involve them in completing this question.

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Question A52 - Ensuring anonymity of identifiable data in publications

- Care should be taken when considering publishing data or case histories to ensure the anonymity of the relevant patients. For example, where tables of data are to be published, care should be taken where the values of cells are small numbers as, in combination with other information, this could render information potentially identifiable. Particular care needs to be taken in relation to 0 as this can create an inference in relation to other cells. For further information on this, please see the Office for National Statistics (ONS) guidance at: <http://www.ons.gov.uk/ons/guide-method/best-practice/disclosure-control-of-health-statistics/index.html> .
- In relation to case histories care should be taken that the combination of incidental details e.g. details about occupation, location, age and ethnicity, do not lead to individuals being identifiable.

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Question A53 - Informing participants of the results>

- It is good practice to disseminate the results of research to research participants and other interested groups or communities. This provides feedback to participants on the outcome of research towards which they have contributed. Consideration should be given to providing a summary sheet of the findings or letting participants know where they can access the results.
- In addition, it may be important to inform patient groups or communities of any findings that are relevant to future care.
- Information about publication arrangements should be included in the participant information sheet.

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Question A54 - Scientific critique

Applicants should tick at least one checkbox and enter further information in the free text box provided. The free text box should include the justification and describe the review process and outcome. If the review has been undertaken but not seen by the researcher the the free text box should be used to give details of the body which has undertaken the review.

- The sponsor of the research is responsible for the assessment of the scientific quality of the proposed research. The research proposal must be subjected to review by experts in the relevant fields able to offer independent advice on its quality. Arrangements for review should be commensurate with the scale of the research and the potential risks or burdens involved for participants.
- Protocols should already have been subjected to scientific critique before formal applications to conduct research are submitted. Exceptions may be permitted if there is a satisfactory explanation.
- Please support your answer by explaining the nature of the review process. A copy of any available comments or scientific critique reports from referees or review committees should be enclosed with the application, together with any correspondence which explains how issues raised by scientific critique have been resolved.
- In the absence of any evidence of scientific critique, the REC may require such an assessment

to be arranged by the applicant or sponsor before confirming its final opinion on the application. The 60 day clock for the ethical review will stop during this process. Alternatively the REC may issue an unfavourable opinion and advise that scientific critique should be obtained before a fresh application is submitted.

- It is recognised that *student research* has an educational and training value, and proposals (especially from undergraduates) will not necessarily be of the same importance or scientific quality as those submitted by professional researchers. However, research proposals from students should be reviewed at least by the academic supervisor. Review bodies will expect the academic supervisor to sign the declaration in Part D of IRAS. This provides assurance that the proposal has identified a valid research question and is suitably designed taking into account the limitations of time and resources.

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Question A55 - Assessment by Expert Advisory Group and CHM

- If your clinical trial falls into the category of trials that require advice from EAG/CHM (see also Question {QNumber(Q_A_16)}), please give details of the status of the application to MHRA for Clinical Trial Authorisation and, where applicable, any changes made to the proposed trial in the light of the expert advice. Any relevant correspondence with the MHRA should be enclosed with the REC application.
- Consider carefully when to make a submission for ethical review. You may opt to apply either sequentially or in parallel. The following points should be considered:
 - It is possible that for trials involving higher risk compounds, advice from EAG/CHM will lead to changes in your protocol, with potential implications for ethical review. If you apply to the REC prior to having received EAG/CHM advice, you must notify the REC promptly of any changes made that may be relevant to the ethics application.
 - In general, a sequential process may be preferable; consider whether factors such as the novelty of the compound including its mode of action and target, the relevance of animal models and the completeness of the data package available may result in protocol changes following EAG/CHM review.
 - Making sequential applications to EAG/CHM first, followed by ethics, allows the REC to receive the final version of the protocol and be fully informed about the outcome of the CTA application when undertaking its review.
- The Commission on Human Medicines (CHM) will require certain information when you

make an application for First-in-Human trials with novel compounds, and applications for trials with integrin antagonists. The details are published on the MHRA's website: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=986

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Question A56 - Statistical review

- Assurance should be provided that the statistical aspects of the protocol have been reviewed by an individual or a department with relevant expertise.
- Any person involved in providing expert statistical advice should be satisfied that they have the necessary expertise, taking into account the nature of the research and the methodology involved. Statistical advice may be provided by one of the investigators or key collaborators named on the application form, provided that they have relevant expertise.
- The individual providing statistical advice should normally be named. If he/she has provided advice in confidence, the name of the department and institution should be given.
- If it is not clear to a review body that the individual statistician or department concerned has relevant expertise, it may request sight of a CV or contact the statistician or department directly to seek clarification of their qualifications and experience.
- If the statistical aspects of the protocol are based on expert advice and appear sound, RECs will usually accept this without requirement for further review. If expert advice has not been sought and/or the REC has doubts about the statistical soundness of the protocol, it may request that the Chief Investigator obtains independent statistical review as part of the request for further information after the REC meeting. Alternatively the REC may commission its own review.
- In the case of *undergraduate research* using simple designs, it will normally be acceptable for statistical advice to be provided by the academic supervisor or another person with expertise in research methodology.

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Question A57 - Primary outcome measure

- In quantitative research, the primary outcome measure takes the form of a statement expressing how, in numerical terms, the primary objective of the study will be met from the data collected. For example, in a study of hypertension, the primary outcome measure might be the systolic blood pressure at the final visit.

There should normally be only one primary outcome measure, though exceptionally there may be more.

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Question A58 - Secondary outcome measures

- Statements expressing how, in numerical terms, other results of the study will be determined from the data collected. There may be no secondary outcome measures, or one, or more than one.

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Question A59 - Sample size

- The sample for the research may include "participants" who are not approached but whose records or samples are to be studied.
- The number of participants is an ethical and methodological issue in any study. The number should be sufficient to achieve worthwhile results but should not be so high as to involve unnecessary recruitment and burdens for participants.
- In the case of research involving qualitative methods only, it is recognised that the number of participants may be small and will not be determined using a statistical power calculation. However, reviewers will find it helpful to know who you are targeting and why you are targeting them. Describe the sampling approach that will be used (theoretical, purposive, snowball, convenience sampling, etc) and give a rationale. Indicate the basis for deciding on the required number of participants and why this number will result in data saturation.
- If a formal sample size calculation is used, this should refer to the primary objective, or in the case of more than one primary objective, the one giving rise to the largest sample size. Sufficient information should be given to allow review bodies to reproduce and check the calculation.
- Sample size calculations will typically involve the following steps:
 - In the case of a *comparison between two or more groups*, the calculation should include the significance level and power of the test to be carried out, as well as stating and justifying the difference in the primary outcome to be detected between the groups. It is important that the difference is not unrealistically high as this could lead to an underestimate of the required sample size.

- For a *single-group study*, the sample size should be justified by reference to a confidence interval (normally 95%), e.g. around the mean of the primary outcome measure.
- If a more complex study design is chosen, for example seeking to show that two groups' responses are equivalent, specialist advice will be needed.
- The number of participants may have been decided pragmatically rather than by a formal calculation, for example where a rare disease is being studied, or where study resources are limited. If this is the case, any limitations that have restricted the sample size should be stated, e.g. what size of effect can be detected for the given power and significance.

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Question A61 - Randomisation

- It is helpful to give the intended mechanism of randomisation, for example a sequence of opaque envelopes, or telephone or internet randomisation. It should be evident to reviewers that the concept of random allocation has been correctly understood, and will be seen to be free from bias.

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Question A62 - Methods of analysis

- For studies with a quantitative (numerical) outcome, give details of the methods that will be used to obtain the results for the primary and secondary outcomes, including methods of summarising the data with numbers and graphs, and the main statistical tests to be used where comparisons are to be made. It is not necessary to give every detail in advance.
- Describe how you will handle missing data, for example due to withdrawal or non-compliance.
- For studies using qualitative methods, researchers should:
 - Outline in simple terms exactly how the data from the study will be managed and analysed. For example, will it be arranged into themes? If so, will this be done by use of a qualitative data analysis tool, by manual analysis and coding of the data, or by some other means? You should state why this is your chosen method of analysis. Give a brief description of any techniques to be used (e.g. framework, content or thematic analysis) for the benefit of lay members. Refer to any qualitative data

software to be used.

- Indicate whether or not member checking will be used (with a brief explanation of what this means for the benefit of lay members). Member checking is not essential but is good practice. Alternatively, you can ask others who are part of the study or independent researchers to check your themes and categories to make sure you have not over-represented some aspect of your data.

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Question A63 - Other key collaborators

- Give names of any other key collaborators of the Chief Investigator or key members of the CI's research team. All co-holders of grants or protocol co-authors should be named. (N.B. Do not include researchers at all the local sites in a multi-centre project – these are to be entered in the Site-Specific Information Form for each site by the Principal Investigator – unless any of them are also a key collaborator at "national" level.) The sponsor of the research is responsible for ensuring key researchers involved in the research have the relevant experience and expertise.
- Where the CI or any of the key collaborators named at A63 are members or deputy members of an ethics committee, the committee is not permitted to review the application. Advice should be sought from the REC concerned or from NRES operational management about arrangements to allocate the application to another REC.

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Question A64-1 -

- The sponsor is the individual, company, institution or organisation, which takes on ultimate responsibility for the initiation, management (or arranging the initiation and management) of and/or financing (or arranging the financing) for that research. The sponsor takes primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.
- Any research requiring the collaboration of the NHS/HSC must have an individual or organisation willing and able to take on the responsibilities of the research sponsor. The responsibilities of sponsors are set out in the UK Policy Framework (see: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/>)
- Any research outside the NHS/HSC should also have a sponsor to take on the specific responsibilities of the role.

- The sponsor is usually, but does not have to be, the main funder of the research. It can also, for example, be the employer of the Chief Investigator, the educational institution (e.g. for student research), or the care organisation where the research is to take place.
- The prospective sponsor(s) must be named in this section. You should contact your R&D office for advice about sponsorship issues before submitting the application.
- It is possible that the duties of the sponsor could be shared between more than one party. If this applies, please enter as the "lead sponsor" in A64-1 the one nominated to receive copies of correspondence from review bodies relating to the application. Please ensure you:
 - Select a status using the radio button selections
 - Enter the commercial status using the drop down options
 - Enter at least the following information for the contact person:
 - Name of organisation
 - Given Name
 - Family Name
 - E-mail
 - Telephone
- Enter further details of the co-sponsors in A64-1 and explain in A64-2 how the responsibilities of sponsorship will be assigned, in particular those relating to monitoring of the research and provision of insurance or indemnity.
- It is your responsibility to ensure that the sponsor(s) are aware of your proposal and accept these responsibilities. An authorised representative of the lead sponsor should complete the sponsor declaration in Part D of IRAS. The person making this declaration does not necessarily have to be an employee of the sponsor, but should be authorised to do so by the sponsor. For example, a Contract Research Organisation (CRO) may be given delegated authority by the sponsor to prepare and submit applications for approval on their behalf.
- Please also complete the box requesting details of a contact point for the lead sponsor and each co-sponsor. The person named must be an employee of the sponsor organisation. The contact for the lead sponsor will often be the same person whose details are entered in A4 as the main contact point for correspondence with review bodies on behalf of the sponsor(s). However, the person named in A4 could be different where responsibilities for managing applications to review bodies have been delegated, for example to a Contract Research Organisation.

Sponsorship of CTIMPs

- For any clinical trial of an investigational medicinal product (CTIMP) it is a legal requirement for the trial to be sponsored.
- If a sponsor of a CTIMP is a commercial or other non-NHS body, a copy of an insurance or indemnity certificate should normally be included with the REC application as evidence of the cover in place for the potential liability of the sponsor. This may be a certificate for a trial

specific policy or a block policy covering a number of trials conducted by the sponsor. If the certificate is not yet available, for example because proposed trial-specific cover will not be brought into effect until the trial is ready to start, the REC will require as a condition of its favourable opinion that a copy of the certificate is provided prior to the start of the trial.

Appointment of sponsor's legal representative in a CTIMP

- If any of the sponsor(s) of a CTIMP is not based in the European Economic Area (EEA), e.g. an American or Japanese company, it is a statutory requirement to appoint a legal representative based in the EEA for the purposes of the trial. Please enter details of the legal representative in the Legal Representative section within A64-1.
- The legal representative:
 - May be an individual person or a representative of a corporate entity
 - Does not have to be a legally qualified person
 - Should be willing to act as the agent of the sponsor in the event of any legal proceedings instituted in the EEA (e.g. for service of legal documents)
 - Should be established and contactable at an address in the EEA
 - Does not assume any of the legal liabilities of the sponsor(s) for the trial by virtue of the role of legal representative and does not therefore require insurance or indemnity to meet such liabilities, but
 - May in some cases enter into specific contractual arrangements to undertake some or all of the statutory duties of the sponsor in relation to the trial, in which case the legal representative would also be regarded as a co-sponsor and would then require insurance or indemnity cover.
- In all cases, evidence should be provided with the application that the legal representative is willing to take on the role of legal representative and is established at an address in the EEA. For example, a copy of correspondence between the sponsor and legal representative on appropriate headed paper could be enclosed, or a copy of a contract.
- Where the legal representative is also a co-sponsor, this should be separately recorded on the application form and details given of the allocation of sponsorship responsibilities. Evidence of insurance or indemnity cover should be provided.

Legal representatives – studies other than CTIMPs

The UK Policy Framework, which has replaced the Research Governance Frameworks, does not require that for **all** studies other than CTIMPs nominate *a legal representative in the UK for the lead sponsor or any co-sponsor who is established outside the UK.*

Clinical investigations of medical devices sponsored by the manufacturer

- Under the Medical Devices Directive 93/42/EEC and the Active Implantable Medical Devices Directive 90/385/EEC, a manufacturer who places devices on the market under their own name and does not have a registered place of business in the European Economic Area, Switzerland or Turkey must designate an Authorised Representative, who does have a registered place of business in the EEA, Switzerland or Turkey, to act on their behalf. Details of the Authorised Representative must be notified to the Competent Authority and placed on the labelling of the device.
- In the case of non-CE marked medical devices, the Medical Devices Directive does not require a manufacturer to appoint an Authorised Representative until the point that the device is placed on the European market. However, the Authorised Representative may be appointed in advance of CE marking at the manufacturer's discretion.
- **If the manufacturer has appointed an Authorised Representative at the time of application to undertake research on the device, details should be included in Part B Section 2 of IRAS.**
- **The role of an Authorised Representative under the Medical Devices Directive is not the same as that of a legal representative for research undertaken on the device in the UK (see previous section of this guidance).** Therefore, non-UK manufacturers acting as sponsors of research in the UK would still need to appoint a legal representative established in the UK, even though they may have appointed an Authorised Representative elsewhere in Europe for the purposes of the Directive.

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Question A65 - Funding

All applications are expected to tick at least one check box.

- The information required here is the funding of the project costs of the researcher (which might include a contribution to salaries, other costs of research staff time, additional equipment and reagents, IT costs, administrative expenses etc). It does not include any funding agreed with the host institution through a research contract to pay for the costs of hosting the research.
- Applicants are strongly advised to secure any project funding required from bodies outside the NHS before submitting the application for ethical review. If funding has not been secured, and the funding body later requires changes to be made to the proposal, these

would require further review by the REC. If the change were major, the REC would require submission of a new application.

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Question A66 - Subcontractors

- The sponsor retains the ultimate accountability for the research. However, if responsibility for any aspects of the research have been delegated to a subcontractor such as a Contract Research Organisation or Site Management Organisation, reviewers will wish to know this and you should make clear the remit of the delegated responsibility.
- Give the name of the organisation, including the name of a contact person within it. This should be the person reviewers can contact in case of queries.

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Question A67 - Previous rejection of the research by an ethics committee

- If the research has been rejected previously, the REC will wish to see a copy of the unfavourable opinion letter. You should also provide a covering letter explaining how the issues of concern have been addressed in this application.
- It does not necessarily follow that rejection in another country will result in rejection in the UK.

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Question A68-1 - Lead R&D contact

- The lead R&D office should be contacted at the earliest possible stage to advise and support the research through the review and set-up process.
- The lead NHS R&D contact may be the R&D contact for:

- The Chief Investigator's employing NHS organisation
- A partner NHS organisation of the university employing the Chief Investigator
- A main NHS collaborator
- Please ensure you complete the following fields:
 - Forenames/Initials
 - Surname
 - Organisation
 - Work email
 - Telephone

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Details of Local Clinical Research Network (LCRN) partner NHS Organisations can be found at: <http://www.crn.nihr.ac.uk/can-help/funders-academics/gaining-nhs-permissions/help-and-guidance-on-nhs-permissions-2/>.

More information about the National Institute for Health Research (NIHR) Clinical Research Network (CRN) and the services it provides can be found at <http://www.crn.nihr.ac.uk/>.

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Question A72 - Host organisations

- Give the number of each type of research site you plan to involve in the study, even if you have not yet approached them.
- A research site is defined as the single organisation responsible for conducting the research at a particular locality. Where the research will be conducted at more than one location within the same organisation (for example, where the departments or clinics involved are dispersed at different hospitals within an acute Trust or Health Board), this should normally be considered as a single site.
- Research sites are organisations responsible for participant-related research procedures specified in the protocol - including recruitment and informed consent. Referral of a patient

for assessment and possible recruitment is not part of the conduct of the study. The following are not considered to be research sites:

- Clinicians or clinical units making referrals to the research team.
- Research units undertaking support functions, e.g. project management, site monitoring, data analysis or report writing.
- For further guidance on research sites, see Section 5 of the Research Ethics Committee (REC) Standard Operating Procedures: <http://www.hra.nhs.uk/resources/research-legislation-and-governance/standard-operating-procedures/> .

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Question A73-1 - Identification of participants

- Any organisations involved only in identification of potential participants are described as "participant identification centres". If any of these centres are NHS organisations, details should be entered in Part C of IRAS.
- For NHS participant identification centres, describe the use of staff, time and resources at each participant identification centre and the arrangements for covering these costs. Please estimate the time that will be taken to identify potential participants for the study at each centre. Include the time taken to send letters of invitation or provide information to potential participants.

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Question A74 - Monitoring and auditing research

- It is the responsibility of the research sponsor(s) to ensure arrangements and systems are in place for the management and monitoring of research. Particular tasks within this responsibility may be delegated to particular individuals or organisations.
- The arrangements for monitoring and auditing the conduct of the study should reflect the allocation of responsibilities set out in the Research Governance Framework.
- In the case of CTIMPs, sponsors and investigators have statutory obligations relating to

pharmacovigilance under Part 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004.

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Question A75-1 - Data Monitoring Committee

- For certain kinds of clinical trial, for example those with predicted high morbidity or mortality, or double-blind trials with unknown or uncertain risks, sponsors are strongly recommended to establish an independent Data Monitoring Committee (sometimes called a Data Safety and Monitoring Committee) to advise on safety issues. A DMC is usually composed of statisticians and clinical investigators not directly involved with the trial. The DMC is responsible for reviewing the data and performing interim analyses.
- For such trials, stopping rules relating to toxicity or outcome should also be considered and agreed with the DMC.
- A detailed Guideline on Data Monitoring Committees was issued in July 2005 by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and is available at:
<http://www.emea.europa.eu/pdfs/human/ewp/587203en.pdf>

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Question A76-1 - Liability arising from the management of the research

- The liabilities of the sponsor relate to the overall management of the study, i.e. the systems and processes through which the sponsor meets its responsibilities. (See guidance on sponsorship at A64-1.) This could include responsibilities for monitoring and training, for example.
- Normally the sponsor(s) will hold insurance or provide indemnity to cover their liabilities as sponsors. Where the sponsor is the employer of the Chief Investigator this is likely to be covered through insurance or indemnity for employer's liability. Where there is more than one sponsor, details for all sponsors should be provided. You should make sure that you have discussed the study with the sponsor and that they have agreed, in principle, to act as sponsor.
- If an NHS organisation is a sponsor, then indemnity is provided through NHS schemes. Tick the response to indicate that NHS indemnity will apply - no proof of indemnity needs to be provided.

- If a university or higher education institution is a sponsor, tick the response to indicate that other insurance or indemnity arrangements will apply and give details. A copy of the relevant policy must be provided.
- If a company is a sponsor, tick the response to indicate that other insurance or indemnity arrangements will apply and give details. A copy of the relevant policy must be provided.
- Where sponsor activities are delegated to sites or sub-contracted to another party, the contract or agreement between the organisations should set out the responsibilities of the parties and the arrangements for covering any liabilities. The sponsor is responsible for ensuring that these arrangements are in place.

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Question A76-2 - Liability arising from the design of the research

- The design of the research is the responsibility of the author and any co-authors of the protocol. Employers are responsible for the actions of their staff who design research studies as part of their employment.
- Normally the employer(s) of the author(s) will hold insurance or provide indemnity to cover their liabilities for the design of the research.
- The main author will usually be the Chief Investigator in the UK. For some international studies it may be the co-ordinating investigator for the study as a whole.
- Where the employees of an NHS organisation are responsible for designing the study, indemnity is provided for harm arising from the design of the study through NHS schemes. Tick the response to indicate that NHS indemnity will apply - no proof of indemnity needs to be provided.
- If the author is employed by a university, or the design of the research has been undertaken in the course of an honorary arrangement with a university, tick the response to indicate that other insurance or indemnity arrangements will apply and give details. This situation applies to researchers employed by a university, regardless of whether or not they hold any honorary contract with an NHS organisation. The university is likely to hold insurance that is additional to normal employer's liability insurance, to cover CTIMPs or other interventional trials. For other non-interventional clinical research, employer's liability insurance is likely to be sufficient. A copy of the relevant policy must be provided.
- If the author is employed by a company, is self-employed or is an independent contractor, tick the response to indicate that other insurance or indemnity arrangements will apply and give details. A copy of the relevant policy must be provided.

Question A76-3 - Liability arising from the conduct of the research

- The conduct of the research refers to the study procedures, as described in the protocol or proposal, which are conducted by the research team with participants, data or tissues.
- Employers are normally responsible for the actions of their staff who conduct research procedures as part of their employment.
- However, where the research involves NHS patients under the care of NHS organisations (including independent contractors), indemnity for harm to participants resulting from clinical negligence is provided either through NHS schemes or through professional indemnity. Formal permission from the NHS organisation (R&D approval) must be obtained in writing before the start of the research. Tick the response to indicate that NHS or professional indemnity will apply - no proof of indemnity needs to be provided.
- Independent contractors, e.g. GPs, should ensure that their professional indemnity provides cover for the activities they will be undertaking.
- Where the research involves private patients under the care of an independent contractor, the main REC requires assurance that appropriate indemnity arrangements will be in place before the study starts. Tick the response to indicate that non-NHS sites are involved and give details of the insurance or indemnity arrangements that will apply. A copy of the relevant policy must be provided.
- Where the investigator is an employee or contractor of a university or Higher Education Institution (HEI) and the research involves members of the public taking part in research outside the care of the NHS, the HEI should have insurance or indemnity to meet the investigator's liabilities. Such research may take place in the HEI, in the community or in other private or state institutions. Tick the response to indicate that non-NHS sites are involved and give details of the insurance or indemnity arrangements that will apply. In some cases, the HEI may need to arrange additional insurance. A copy of the relevant policy must be provided.
- Where the investigator is an employee or contractor of a Contract Research Organisation or Site Management Organisation and the research is taking place through a commercial organisation, the company should have insurance or indemnity to meet the investigator's liabilities. Tick the response to indicate that non-NHS sites are involved and give details of the insurance or indemnity arrangements that will apply. A copy of the relevant policy must be provided.

A76-5 Industry guidelines on compensation and insurance arrangements for Phase 1 trials

- The Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA) and the Clinical Contract Research Association (CCRA) have jointly published guidance on insurance and compensation for Phase I clinical trials. This is available at: <http://www.abpi.org.uk/our-work/library/guidelines/Pages/clinical-trials-insurance.aspx>
- The guidance, which has been developed in consultation with NRES and the Department of Health, is for trials including first-in-man studies involving healthy volunteers.
- The guidance also applies to studies conducted in patient volunteers without the target disease to provide additional pharmacokinetic data about the medicine under research.

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A76-5

Insurance policies of all types invariably contain appropriate conditions and clinical trial insurance policies are no exception. The following conditions for liability are normal, but are unlikely to be an issue in practice in the specialised field of clinical trial insurance:

- Absence of intentional misconduct on the part of the insured;
- Meeting the regulatory requirement that the study be authorised by the competent authorities;
- Making proper disclosure of background facts of the proposed study that would be material to the insurer's willingness to accept the risk or his setting of the premium;
- Making timely notification of a claim to the insurer and not compromising it without the agreement of the insurer.

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Question A77 - Compensation for harm where liability does not arise

- This question addresses the possibility of compensation where no legal liability arises for any person, e.g. a participant has suffered harm as a result of taking part in the research but there has been no negligence in its management, design or conduct and no other liability arises such as product liability. This compensation is commonly known as "no fault compensation".
- Sponsors are not obliged to offer no fault compensation in all cases. The REC will inform you if they consider that provision for no fault compensation is needed.

Commercially sponsored trials

- In the case of commercially sponsored CTIMPs or medical device studies, arrangements for no fault compensation will normally be provided in accordance with the Association of British Pharmaceutical Industry (ABPI) or Association of British Healthcare Industry (ABHI) schemes. Tick the response to indicate that arrangements for compensation have been made, and confirm that the ABPI/ABHI guidelines will be followed. A copy of the form of indemnity (unsigned) to be used should be enclosed with the application.

Non-commercial research

- In the case of non-commercial research, arrangements for no fault compensation cannot be made in advance by the NHS or other public bodies (e.g. MRC). Such organisations, although not accepting liability, may consider making an ex gratia payment on a voluntary basis in the event of a claim.
- Some Higher Education Institutions may choose to provide no fault compensation for research involving their employees. If this is the case, tick the response to indicate that arrangements for compensation have been made. A copy of the policy should be provided.
- Where no organisation has arranged or is able to provide no fault compensation, tick the response to indicate that no arrangements for compensation have been made.

Information for participants

- Before agreeing to take part, participants should be made aware of any provision (or lack of provision) for no fault compensation. If no such provision is available, participants should be aware that in the unlikely event of a claim, for which negligence could not be demonstrated, they might need to take legal action for which they would need to pay.
- Health Research Authority (HRA) guidance on the participant information sheet is available at: <http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/>

REC responsibilities

- For non-commercial research, there are no guidelines on whether provision for no-fault compensation should be in place. It is an ethical issue for the sponsor and the REC to consider on a case by case basis, taking into account the potential risk to participants. In most studies this will not be necessary.
- The REC may decide that participants should be protected by no fault compensation arrangements. If so, the research could go ahead only if a body was willing and able to make

provision for compensation, backed by adequate insurance or indemnity arrangements.

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Question A78 - Intellectual property

- Intellectual Property is the tangible output of any intellectual activity that is new or previously un-described. It has an owner; it can be bought, sold or licensed and must be adequately protected. It can include inventions, industrial processes, software, data, written work, designs and images.
- Any research which could potentially lead to intellectual property rights for you or your employer should be discussed with your employer and the lead NHS R&D office as early as possible in the planning of the research.

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Part B Section 1: Medicinal Products

Part B Section 1: Medicinal Products

- This section provides information for the application for the application to MHRA Medicines.
- Information on IMPs to be used in the trial are included in the REC and R&D forms. It is not necessary to include a copy of the whole EudractCT application with applications to RECs or R&D offices.

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Question 14 - This question applies to sites where the qualified person certifies batch

- This question applies to sites where the qualified person certifies batch release in accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medicinal Products in the European Union

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Question 15-1 - Product Name

- To be provided only when there is no trade name. This is the name routinely used by a sponsor to identify the IMP in the CT documentation (protocol, IB, ...).

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Question 15-1 - Product Code

- To be provided only when there is no trade name. This is a code designated by the sponsor which represents the name routinely used by the sponsor to identify the product in the CT documentation. For example, a code may be used for combinations of drugs or drugs and devices.

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Question 15-1 - Anatomical Therapeutic Chemical (ATC)

- Available from the Summary of Product Characteristics (SmPC).

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Part B Section 2: Medical Devices

Question 1 - Manufacturer

- If the manufacturer of the medical device under investigation is the same person named as lead sponsor in Question A64-1, answer Yes and the details will be populated. If the manufacturer is a different person, please answer No and give full details.
- "Manufacturer" means the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.
- In cases where the investigational medical device will be CE marked and placed on the market under the name of a third party who is yet to be identified, the organisation that is responsible for developing the device and is undertaking the clinical investigation should sign this statement.

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Question 2 - Details of medical devices

- Please provide details of the manufacturer. For all commercially manufactured devices, please give the manufacturer's trade name associated with the device.
- Please provide details of both the device identification name and number used by the manufacturer and the generic name used to describe the principal intended use of the device.
- If you will be studying more than one medical device, please give details of each device. Click on the button to "*Add another investigational device*" if applicable.
- There is no need to give details in this section of accessory devices used in the research, which are not the subject of investigation.
- Where applicable, please give the approximate length of time since the device came into clinical use in the UK. For clinical investigations of non-CE marked devices requiring notification to the MHRA, please answer N/A.

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More than one investigational device?

- This button can be used to create additional fields where more than one medical device is under study.

Clinical investigations

- For any clinical investigation requiring notification to the Competent Authority, please give details of each investigational medical device. This includes any CE marked medical devices that are being used for a new purpose in this clinical investigation and all medical devices that are not CE marked.

Research study of CE marked device

- Please give details of each medical device under study. For example, in a comparative study of more than one CE marked device, give details of all products including any used as controls.

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Question 1 - First submission to MHRA or re-submission?

- Re-submission should only be selected in cases where a manufacturer is re-submitting an application which has previously been objected to by MHRA.
- If this is the case, please provide the MHRA reference number for the previous submission to which MHRA objected.

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Question 3 - Notified Body approval of quality system or process

- If a Notified Body has been appointed by the manufacturer of the investigational device please provide the 4 digit reference number unique to the Notified Body appointed and provide details of the scope of the certification issued by the Notified Body.

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Question 4 - Class of device

- General Medical Devices - this should be the classification of the device which has been determined using the Classification Rules in Annex IX of the Medical Devices Directive 93/42/EEC.
- Active Implantable Medical Devices – please select AIMD.

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Question 5 - Multi-country investigations

- If this is part of a multi-country clinical investigation, please give details of other countries that will be or have been approached.
- This should include all European and Non-European countries.

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Question 6 - Number of devices in the trial

- Please give the number of devices that will be available in the UK clinical trial and the total global number if the trial is multi-country.
- If there is more than one investigational device, please state the total number and then give the breakdown between each device in the "further details" boxes.

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Question 7 - Single site or multi-site trial?

- Please indicate whether this will be a single site or multi-site trial in the UK. This question is only applicable to the number of sites in the UK.

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Question 9 - Additional Clinical Investigators

- Please provide details of **all** UK investigators, other than the Principal Clinical Investigator, who will be participating in this clinical trial. Include each clinical investigator where there is more than one investigator at a site.
- The Principal Chief Investigator will normally be the same person named as "Chief Investigator" for the purpose of the REC application.

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Question 10-1

Substance or human blood derivative referred to in Section 7.4 of Annex 1

- This should be signed by an appropriate employee of the manufacturer of the medical device under investigation or the authorised representative appointed by the manufacturer.

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Question 10-2 -

Active Implantable Device

- Please indicate whether the device(s) under investigation falls under the Active Implantable Medical Devices Directive 90/385/EEC.

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Question 10-3 - Tissue of animal origin

- This statement is only applicable to devices falling under the Medical Devices Directive 93/42/EEC, as amended by 2007/47/EC, and should be signed by an appropriate employee of the manufacturer of the medical device under investigation or the authorised representative appointed by the manufacturer.

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Part B Section 3: Ionising Radiation

Part B Section 3: Ionising Radiation

- The design of this section of IRAS and the accompanying guidance have been drawn up in consultation between the following bodies:
 - Health Protection Agency, Medical Exposure Department (HPA-RPD-MED) on behalf of DH
 - British Institute of Radiology (BIR) – Radiation Protection Committee
 - Institute of Physics and Engineering in Medicine (IPEM) – Special Interest Groups for diagnostic radiology, radiation protection and nuclear medicine
 - Royal College of Radiologists
 - British Nuclear Medicine Society
 - Society of Radiographers
 - Administration of Radioactive Substances Advisory Committee (ARSAC)
 - NHS R&D Forum
 - National Research Ethics Service (NRES).
- Part B Section 3 of IRAS is divided into two parts, relating to radioactive materials and other ionising radiation respectively.
- Where the research involves administration of radioactive materials which are additional to normal care, nuclear medicine professionals at each site will require a research ARSAC certificate.
- The risk assessment should be completed with input from health professionals with the appropriate expertise to act as the lead Medical Physics Expert (MPE) and lead Clinical Radiation Expert (CRE) for the purposes of the application. Where the research involves different modalities and requires input from other experts, the lead experts should incorporate their advice into a single combined assessment.
- The information provided in this section should cover the potential range of exposure at all study sites participating in the research.

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Question A1 - Details of radioactive materials

- Please provide full information about each radioactive material being used. Where there is more than one radionuclide, generate a separate table.
- Notes on the table:
 - Investigation: the investigation employing radioactive materials which is included in the study protocol.
 - Radionuclide: the material which will be used.
 - Proposed activity: the quantity which will be used in an individual investigation expressed in Microbecquerels (MBq).
 - Route: the route by which the material will be given, e.g. intravenous, oral.
 - Number of administrations: the number of individual investigations specified by the protocol for each study participant.
 - Effective dose or target tissue dose: refer to Annex II of the ARSAC Notes for Guidance, available at <http://www.arsac.org.uk/>
- The information should match the information about these investigations included in Question 19 of Part A of IRAS ("Details of clinical interventions and procedures").

The HRA provides a free e-learning module on research involving exposure to ionising radiation which can be accessed from their website [here](#).

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Question B1 Details of other ionising radiation

- Provide full information about any other ionising radiation not listed in A1, i.e. other than radioactive materials. List each procedure required in the study protocol and, against each, specify:

- Number of procedures: the number of individual examinations specified by the protocol for each study participant
- Estimated procedure dose: the estimated dose per examination calculated by the lead MPE.
- The information should match the information about these investigations included in Question 19 of Part A of IRAS ("Details of clinical interventions and procedures").

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Questions C1-C3 - Dose and risk assessment

Identifying a lead Medical Physics Expert (MPE)

- The role of lead Medical Physics Expert should be undertaken by a MPE who is a registered health professional and has expertise relevant to the proposed procedures. MPEs are usually registered as clinical scientists by the Health Professions Council under the Health Professions Order 2001.
- The Chief Investigator may wish to approach a colleague at the lead site to undertake the role of lead MPE. If a suitable individual is not available, it is acceptable for the role to be undertaken by a registered health professional at another research site or who is not involved at any site, provided they are suitably qualified. It is the responsibility of the Chief Investigator to ensure that the person appointed has appropriate expertise.
- Where more than one modality (imaging method) is involved, advice from more than one MPE may be required. The lead MPE should produce a combined assessment, giving the names of any other MPEs who have contributed to the assessment in Question C1.
- It is not essential for the lead MPE to be independent of the research team.
- It is not essential for the lead MPE to be employed by the NHS. The role may be undertaken by a suitably qualified registered health professional working in the private sector.
- However, the lead MPE should always be professionally based in the United Kingdom, as the role requires expertise in the UK regulatory and clinical environment.

Assessment by the lead MPE

- The lead MPE should perform a dose/risk assessment of the proposed investigations for inclusion in sub-section C1. It is helpful if the MPE has seen a copy of the lead CRE's clinical assessment beforehand.
- It is important that the assessment is included in the on-line form rather than submitted in

enclosures. This will facilitate access to the information by NHS R&D offices and radiation professionals at each research site. In the case of radioactive materials, the assessment will also be populated to the ARSAC research application form.

- The lead MPE should calculate appropriate doses for the proposed examinations, estimating the Total Research Protocol Dose and the element that is potentially additional to normal clinical exposure. The assessment should also include information about risks to facilitate the REC's deliberations as follows:
 - ◊ Risks should be quantified where possible, referencing risk co-efficients used (e.g. HPA, ICRP).
 - ◊ The risk assessment should take into account the population being irradiated. Any adjustments made to these co-efficients (e.g. to take account of a paediatric cohort) must be clearly stated. Any risk model used should be referenced (e.g. BEIR VII).
 - ◊ The clinical prognosis of the study cohort should be taken into account when assessing risk, either following a risk calculation that excluded prognosis to place the risk in context, or as part of the risk assessment model.
 - ◊ A risk statement should be included that gives an appropriate risk comparator, i.e. compares a radiation risk with an activity that has an appropriately similar level of risk.
- The lead MPE may also advise the Chief Investigator on the explanation of risks in the participant information sheet, practical aspects of the examinations, additional statutory requirements and any resource/organisational issues at research sites.
- The dose assessment should facilitate local IRMER compliance at participating sites by:
 - ◊ Setting a Total Research Protocol Dose (TRPD) for the whole study.
 - ◊ Assessing additional radiation dose based upon the lead CRE's statement on normal/additional exposures.
 - ◊ Using national Diagnostic Reference Levels (DRLs) for examination dose where available, or an estimated dose to a standard patient. Where estimated, the methodology must be stated.
- Under IRMER, it is the role of the local MPE at each site to help establish the dose constraint or target dose level. However, the assessment by the lead MPE will facilitate this process by proposing for ethical approval an approximate total dose for an average patient for the whole study (TRPD), along with an order of magnitude risk from this dose. This will establish a level of exposure that is ethically acceptable while allowing for reasonable variation around this level.
- It is therefore important for the lead MPE to take account of potential variations in dose arising from differences both in examination protocols and in what constitutes normal practice among participating UK sites, using DRLs where appropriate. This will ensure that the main REC is fully appraised of the potential additional radiation burden to participants and how it

may vary from centre to centre. The lead MPE may wish to consult colleagues at other sites that will be taking part in the study.

- Where the study involves changes in therapeutic dose or volume delivered, the lead Clinical Radiation Expert (CRE) will advise on the expected therapeutic outcome compared to standard protocols. The lead MPE can also provide relevant patient dosimetry advice and predictions of radiobiological effectiveness of all additional exposures associated with a patient treatment which does not follow standard protocols, even if the therapy dose itself does not change. The assessment should include consideration of doses as part of the treatment planning process (for instance an imaging modality such as PET CT for tumour delineation) or the verification process (such as Image Guided Radiotherapy).
- The lead MPE's assessment should be copied to the lead CRE, who should check that his/her advice remains valid in the light of the detailed dose and risk assessment.

Radioactive materials – rare or unusual substances

- If it is proposed to administer rare or unusual radioactive substances the following information is required by ARSAC and should be included in the dose/risk assessment:
 - ◊ The formula of the substance and the site of its label.
 - ◊ A summary of the animal (and any human) experiments and the bio-distribution data obtained.
 - ◊ A description of the method use in estimating the effective dose.

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Questions D1-D3 - Clinical assessment

Identifying a lead Clinical Radiation Expert

- The lead CRE should be a registered health professional with clinical expertise in the modality (imaging method) involved in the study. For radioactive materials exposure this will typically be a Nuclear Medicine Specialist. For other ionising radiation the CRE could be a radiologist or a clinical oncologist (for radiotherapy).
- The CI will often wish to approach a colleague at the lead site to undertake the role of lead CRE. If a suitable individual is not available, it is acceptable for the role to be undertaken by a registered health professional at another research site or who is not involved at any site, provided they are suitably qualified to give expert advice. It is the responsibility of the CI to ensure that the person appointed has appropriate expertise.

- Where the study involves different types of exposure (for example, both radiotherapy and other ionising radiation), advice may need to be sought from other CREs with relevant expertise. The lead MPE should produce a combined assessment, giving the names of any other CREs who have contributed to the assessment.
- It is not essential for the lead CRE to be independent of the research team.
- It is not essential for the lead CRE to be employed by the NHS. The role may be undertaken by a suitably qualified registered health professional at a private hospital or independent sector treatment centre.
- However, the lead CRE should always be professionally based in the United Kingdom, as the role requires expertise in the UK regulatory and clinical environment.

Assessment by lead CRE

- The Chief Investigator should submit a draft of the application form, study protocol and participant information sheet to the lead CRE(s) who should:
 - ◊ Review the proposed investigations/procedures (as summarised in question A19 in IRAS and in Questions A1 and B1 in this section)
 - ◊ Assess whether the exposures in the protocol would exceed the exposures performed under existing clinical protocols as part of normal clinical management *at any site in the study*
 - ◊ Where additional exposures could be involved, give advice in sub-section D2 on their suitability to the objectives of the study and ethical acceptability.
- It is important that the assessment is included in the on-line form rather than submitted in enclosures. This will facilitate access to the information by NHS R&D offices and radiation professionals at each research site. In the case of radioactive materials, the assessment will also be populated to the ARSAC research application form.
- In undertaking the assessment, the lead CRE should consider:
 - ◊ The specific objectives of the exposure and the characteristics of the research population
 - ◊ The potential diagnostic or therapeutic benefits, including direct benefits to the participant and the benefits to society
 - ◊ The potential diagnostic or therapeutic benefits, including direct benefits to the participant and the benefits to society
 - ◊ The detriment to participants that the exposure may cause
 - ◊ The availability of alternative techniques involving less, or no, exposure to ionising radiation

- The possibility that participants will be participating in other trials involving additional radiation. (Refer to questions 17 and 32 in Part A of IRAS for the selection criteria and details of possible involvement in other research.)
- The characteristics of the research population will include such factors as the age of the participants and their likely life expectancy.
- For multi-site trials, variations in normal practice around the UK will have a bearing on whether or not the planned exposures represent an *additional* radiation burden for participants. The lead CRE should take such variations into account in making his/her assessment. Where any additional exposure is involved in the study, the assessment should provide a quantitative estimate of the range of normal/additional exposures across the study sites. To achieve this, it may be helpful to consult Practitioners and Medical Physics Experts at other research sites. Where existing clinical guidelines have been used in reaching a judgement about normal/additional exposures, these should be referenced.

Participant information sheet

- The lead CRE should review the information sheet for participants and ensure that it contains accurate and appropriate advice on radiation exposure. In particular:
 - Where there is no direct benefit to the participant, this should be made clear.
 - The risks are realistic and not over- or under-stated.
 - The information is comprehensible to participants
 - It is sensitive to cohort prognosis by taking into account the population and illness under study
 - "Raw" numerical risks are not quoted without reference to reasonable comparators, and terminology is harmonised by reference to tables such as the HPA table in their patient information leaflet concerning x-rays:
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947388410

Liaison with lead MPE

- The lead CRE should copy the assessment to the lead MPE for the research. Co-operation with the lead MPE during protocol development will ensure that any variations in clinical practice are taken into account by the lead MPE when preparing the dose and risk assessment for ethical review.

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Part B Section 4: Existing Samples

Question 1 - Type of human tissue or other biological material

- Describe the body sites involved and the format in which the samples will be supplied. Indicate if the samples are perishable in nature, their likely deterioration time and the purposes for which they will be used.

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Question 2 - Anonymisation of samples

- Samples will normally not be identifiable where obvious identifiers (e.g. name, address, date of birth) are removed at the point of release. However, consideration should be given to whether donors could be identifiable if viewed in conjunction with other publicly available information. This will depend on the information in the dataset and its rarity. For example, incidence of a rare disease in a woman aged 85 in a known postcode region might be identifiable to anyone with knowledge of the community or access to census data.

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Questions 3 - Consent

Tissue obtained from the living after 1 September 2006

- For tissue obtained from the living after 1 September 2006, section 1(9) of the Human Tissue Act 2004 provides that there is no legal requirement for consent to store or use the tissue for research provided that:
 - ◊ The research is ethically approved (under Regulations this approval must be given by a REC), and
 - ◊ The research is to be carried out in circumstances such that the researcher is not in possession, and not likely to come into possession, of information from which the donor can be identified.
- However, it is best practice to seek consent for use in research wherever possible. It is accepted as good practice to seek "broad consent" to store and use material prospectively in a number of future projects, potentially in a range of research fields. The principle of broad consent has been endorsed in Parliamentary debates during the passage of the Human Tissue

Act 2004 and in the HTA Code of Practice on Consent.

- Where consent has been obtained for use in research, please enclose a copy of the information sheet and consent form used (if available).
- If consent has not been obtained for use in research, consider whether it would be ethically appropriate and feasible to re-contact donors. If you do not propose to do this, please justify.
- Where consent for use in research is not in place, samples must be obtained without information from which donors could be identified by the research team.
- Where consent is to be sought, details of how donors will be identified and approached should be given in answer to Questions A27 and A29. A copy of the information sheet and consent form should be enclosed.

Existing holdings (tissue stored prior to 1 September 2006)

- Under the Human Tissue Act 2004, where tissue was collected and stored prior to 1 September 2006 there is no legal requirement for consent to store or use the samples in research. However, the Human Tissue Authority's Code of Practice on Consent states that "this does not mean that all such human tissue can be used freely and without regard to issues of consent or other ethical considerations" (paragraph 114). The Code gives detailed guidance, to which both researchers and RECs should have regard. It is available at www.hta.gov.uk.
- For purposes of ethical review the REC would find it helpful to know whether or not consent has been given previously and for what purposes. Say whether the consent was project-specific or "broad" consent for storage and use in future research.
- It is always best practice where possible to have consent for the use of tissue samples in research. Where it is proposed not to re-contact donors, this should be justified.
- It is recognised that it may not be feasible to seek further consent in the case of established collections, which were not obtained for the primary purpose of research. It may not be possible to identify or re-contact donors. This could also cause distress in some cases, for example if it reminded patients or their relatives of a serious illness or injury.
- In some cases it may be advisable to re-contact donors, in particular if identifiable samples are to be used and the results could have clinical significance for the donors or their relatives.
- In addition to the interests of donors, ethical review will take into account the potential benefits to future patients and society of allowing such material to be used in the research.

Collections from the deceased

- Under the Human Tissue Act 2004, "appropriate consent" is required to store or use tissue obtained from the deceased after 1 September 2006, unless the person died more than 100

years ago. Appropriate consent should be sought if not already been obtained for use in future research.

- Detailed guidance on consent to store and use tissue from the deceased is given in the Human Tissue Authority Code of Practice on Consent (available at www.hta.gov.uk).
- In the case of a deceased adult, appropriate consent means:
 1. The consent of the deceased person given before death.
 2. If there is no prior consent by the deceased person, the consent of a nominated representative.
 3. If no representative was appointed by the deceased person, a person in a qualifying relationship (see below).
- In the case of a deceased child, appropriate consent means:
 1. A person who had parental responsibility immediately before the child's death.
 2. If no person had parental responsibility, another person in a qualifying relationship.

Qualifying relationship

- Persons in a *qualifying relationship* are ranked in the following order:
 - (a) Spouse or partner (including civil partners)
 - (b) Parent or child
 - (c) Brother or sister
 - (d) Grandparent or grandchild
 - (e) Child of a brother or sister
 - (f) Stepfather or stepmother
 - (g) Half brother or half sister
 - (h) Friend of long standing.
- Where there is more than one person in the same rank in the hierarchy, the consent of any one of them will constitute appropriate consent.
- In the case of consent to analyse DNA or use the results of the analysis for research purposes, the consent of any person in the list above is enough – the list is unranked in this case.

Scotland

- Under the Human Tissue (Scotland) Act 2006, which was implemented on 1 September 2006, authorisation is required to use tissue from a deceased person for research purposes. Detailed guidance on the Act has been issued by the Scottish Executive in HDL(2006)46, which is available on the Scottish NHS website at:

http://www.sehd.scot.nhs.uk/mels/HDL2006_46.pdf

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Questions 4 - Consent

Tissue obtained from the living after 1 September 2006

- For tissue obtained from the living after 1 September 2006, section 1(9) of the Human Tissue Act 2004 provides that there is no legal requirement for consent to store or use the tissue for research provided that:
 - The research is ethically approved (under Regulations this approval must be given by a REC), and
 - The research is to be carried out in circumstances such that the researcher is not in possession, and not likely to come into possession, of information from which the donor can be identified.
- However, it is best practice to seek consent for use in research wherever possible. It is accepted as good practice to seek "broad consent" to store and use material prospectively in a number of future projects, potentially in a range of research fields. The principle of broad consent has been endorsed in Parliamentary debates during the passage of the Human Tissue Act 2004 and in the HTA Code of Practice on Consent.
- Where consent has been obtained for use in research, please enclose a copy of the information sheet and consent form used (if available).
- If consent has not been obtained for use in research, consider whether it would be ethically appropriate and feasible to re-contact donors. If you do not propose to do this, please justify.
- Where consent for use in research is not in place, samples must be obtained without information from which donors could be identified by the research team.
- Where consent is to be sought, details of how donors will be identified and approached should be given in answer to Questions A27 and A29. A copy of the information sheet and consent form should be enclosed.

Existing holdings (tissue stored prior to 1 September 2006)

- Under the Human Tissue Act 2004, where tissue was collected and stored prior to 1 September 2006 there is no legal requirement for consent to store or use the samples in research. However, the Human Tissue Authority's Code of Practice on Consent states that "this does not mean that all such human tissue can be used freely and without regard to issues of consent or other ethical considerations" (paragraph 114). The Code gives detailed guidance, to which both researchers and RECs should have regard. It is available at www.hta.gov.uk.
- For purposes of ethical review the REC would find it helpful to know whether or not consent has been given previously and for what purposes. Say whether the consent was project-specific or "broad" consent for storage and use in future research.
- It is always best practice where possible to have consent for the use of tissue samples in research. Where it is proposed not to re-contact donors, this should be justified.
- It is recognised that it may not be feasible to seek further consent in the case of established collections, which were not obtained for the primary purpose of research. It may not be possible to identify or re-contact donors. This could also cause distress in some cases, for example if it reminded patients or their relatives of a serious illness or injury.
- In some cases it may be advisable to re-contact donors, in particular if identifiable samples are to be used and the results could have clinical significance for the donors or their relatives.
- In addition to the interests of donors, ethical review will take into account the potential benefits to future patients and society of allowing such material to be used in the research.
- Under the Human Tissue Act 2004, "appropriate consent" is required to store or use tissue obtained from the deceased after 1 September 2006, unless the person died more than 100 years ago. Appropriate consent should be sought if not already been obtained for use in future research.
- Detailed guidance on consent to store and use tissue from the deceased is given in the Human Tissue Authority Code of Practice on Consent (available at www.hta.gov.uk).

Collections from the deceased

- In the case of a deceased adult, appropriate consent means:
 1. The consent of the deceased person given before death.
 2. If there is no prior consent by the deceased person, the consent of a nominated representative.
 3. If no representative was appointed by the deceased person, a person in a qualifying relationship (see below).

- In the case of a deceased child, appropriate consent means:
 1. A person who had parental responsibility immediately before the child's death.
 2. If no person had parental responsibility, another person in a qualifying relationship.

Qualifying relationship

- Persons in a *qualifying relationship* are ranked in the following order:
 - (a) Spouse or partner (including civil partners)
 - (b) Parent or child
 - (c) Brother or sister
 - (d) Grandparent or grandchild
 - (e) Child of a brother or sister
 - (f) Stepfather or stepmother
 - (g) Half brother or half sister
 - (h) Friend of long standing.
- Where there is more than one person in the same rank in the hierarchy, the consent of any one of them will constitute appropriate consent.
- In the case of consent to analyse DNA or use the results of the analysis for research purposes, the consent of any person in the list above is enough – the list is unranked in this case.

Scotland

- Under the Human Tissue (Scotland) Act 2006, which was implemented on 1 September 2006, authorisation is required to use tissue from a deceased person for research purposes. Detailed guidance on the Act has been issued by the Scottish Executive in HDL(2006)46, which is available on the Scottish NHS website at:

http://www.sehd.scot.nhs.uk/mels/HDL2006_46.pdf

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Questions 5 - Consent

Tissue obtained from the living after 1 September 2006

- For tissue obtained from the living after 1 September 2006, section 1(9) of the Human Tissue Act 2004 provides that there is no legal requirement for consent to store or use the tissue for research provided that:
 - The research is ethically approved (under Regulations this approval must be given by a REC), and
 - The research is to be carried out in circumstances such that the researcher is not in possession, and not likely to come into possession, of information from which the donor can be identified.
- However, it is best practice to seek consent for use in research wherever possible. It is accepted as good practice to seek "broad consent" to store and use material prospectively in a number of future projects, potentially in a range of research fields. The principle of broad consent has been endorsed in Parliamentary debates during the passage of the Human Tissue Act 2004 and in the HTA Code of Practice on Consent.
- Where consent has been obtained for use in research, please enclose a copy of the information sheet and consent form used (if available).
- If consent has not been obtained for use in research, consider whether it would be ethically appropriate and feasible to re-contact donors. If you do not propose to do this, please justify.
- Where consent for use in research is not in place, samples must be obtained without information from which donors could be identified by the research team.
- Where consent is to be sought, details of how donors will be identified and approached should be given in answer to Questions A27 and A29. A copy of the information sheet and consent form should be enclosed.

Existing holdings (tissue stored prior to 1 September 2006)

- Under the Human Tissue Act 2004, where tissue was collected and stored prior to 1 September 2006 there is no legal requirement for consent to store or use the samples in research. However, the Human Tissue Authority's Code of Practice on Consent states that "this does not mean that all such human tissue can be used freely and without regard to issues of consent or other ethical considerations" (paragraph 114). The Code gives detailed guidance, to which both researchers and RECs should have regard. It is available at www.hta.gov.uk.
- For purposes of ethical review the REC would find it helpful to know whether or not consent has been given previously and for what purposes. Say whether the consent was project-specific or "broad" consent for storage and use in future research.
- It is always best practice where possible to have consent for the use of tissue samples in

research. Where it is proposed not to re-contact donors, this should be justified.

- It is recognised that it may not be feasible to seek further consent in the case of established collections, which were not obtained for the primary purpose of research. It may not be possible to identify or re-contact donors. This could also cause distress in some cases, for example if it reminded patients or their relatives of a serious illness or injury.
- In some cases it may be advisable to re-contact donors, in particular if identifiable samples are to be used and the results could have clinical significance for the donors or their relatives.
- In addition to the interests of donors, ethical review will take into account the potential benefits to future patients and society of allowing such material to be used in the research.

Collections from the deceased

- Under the Human Tissue Act 2004, "appropriate consent" is required to store or use tissue obtained from the deceased after 1 September 2006, unless the person died more than 100 years ago. Appropriate consent should be sought if not already been obtained for use in future research.
- Detailed guidance on consent to store and use tissue from the deceased is given in the Human Tissue Authority Code of Practice on Consent (available at www.hta.gov.uk).
- In the case of a deceased adult, appropriate consent means:
 1. The consent of the deceased person given before death.
 2. If there is no prior consent by the deceased person, the consent of a nominated representative.
 3. If no representative was appointed by the deceased person, a person in a qualifying relationship (see below).
- In the case of a deceased child, appropriate consent means:
 1. A person who had parental responsibility immediately before the child's death.
 2. If no person had parental responsibility, another person in a qualifying relationship.

Qualifying relationship

- Persons in a *qualifying relationship* are ranked in the following order:
 - (a) Spouse or partner (including civil partners)
 - (b) Parent or child
 - (c) Brother or sister

- (d) Grandparent or grandchild
- (e) Child of a brother or sister
- (f) Stepfather or stepmother
- (g) Half brother or half sister
- (h) Friend of long standing.

- Where there is more than one person in the same rank in the hierarchy, the consent of any one of them will constitute appropriate consent.
- In the case of consent to analyse DNA or use the results of the analysis for research purposes, the consent of any person in the list above is enough – the list is unranked in this case.
- Under the Human Tissue (Scotland) Act 2006, which was implemented on 1 September 2006, authorisation is required to use tissue from a deceased person for research purposes. Detailed guidance on the Act has been issued by the Scottish Executive in HDL(2006)46, which is available on the Scottish NHS website at:

http://www.sehd.scot.nhs.uk/mels/HDL2006_46.pdf

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Question 6 - Use of tissues or cells for human application

- Only answer Yes to this question if you will be using tissues or cells for human application in the research, e.g. transplantation.
- Guidance on use of tissues and cells for human application is available from the Human Tissue Authority at: http://www.hta.gov.uk/about_hta/eutcd_information.cfm.

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Question 7 - Licensing arrangements for research involving human application

- Detailed guidance on licensing issues is available from the Human Tissue Authority at: http://www.hta.gov.uk/about_hta/eutcd_information.cfm.

- Review bodies will wish to be assured either that licences are already in place or have been applied for, where this is necessary to comply with the EU Tissues and Cells Directive and the Human Tissue (Quality and Safety for Human Application) Regulations 2007.
- Please contact the HTA directly if expert advice is needed on licensing.

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Question 8 - Types of test or analysis

- Describe the methodologies to be applied to the study of the samples.
- Indicate the nature of the research data that will be generated by these methods.
- Highlight the types of analysis you anticipate may raise ethical questions and how you will deal with such issues.

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Question 9 - Analysis or use of genetic material

- Answer Yes to this question if the analyses may produce information that involves genetic sequence data, single nucleotide polymorphism data, genetic "finger print" data, ploidy data or cytogenetic data, including the detection of mutations or genetic variants.

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Question 10 - Findings of clinical significance

- Indicate whether the analyses described in question 9 could have prognostic, predictive or other significance for individual donors/subjects or their relatives.
- If so, describe the nature of the clinical significance for the individual subjects that might be encountered.

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Question 11 - Arrangements to notify individuals of clinically significant findings

- If No, indicate clearly the reasons why data will not be notified to the participants or their healthcare professionals. For example, the reasons may be based in ethics, practicality or science. Explain how the decision not to provide feedback to participants is consistent with the terms of their consent.
- If Yes, describe how the feedback will be provided – will it be directly to the participant or via a healthcare professional? In either case, please explain how the implications of the feedback will be explained to the participants and how they will be supported or counselled in light of the feedback. If some participants have indicated that they do not wish to receive feedback of clinical significance, how will you deal with this in the light of clinically significant information resulting from the research?

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Question 12 - Holder of the samples

- The question relates to the current holder(s) of the samples (before release to the researcher). The REC will wish to know that the samples are being supplied from a reputable source and that the bank/collection has a Human Tissue Authority (HTA) storage licence (if applicable). Once ethical approval has been obtained, the researcher has lawful authority to store them for the duration of the project.
- If samples will be obtained from more than one tissue bank or collection, please give details of each source.
- The holder of the samples could be a NHS Pathology Department. Where tissue is taken in the course of normal clinical care and is stored as part of a clinical diagnostic archive, storage of that tissue does not require a Licence from the HTA for research. If slivers of tissue taken from blocks stored as part of the diagnostic archive are then used for research, no licence would be needed; the primary purpose for storing the tissue would still be diagnostic.
- The licensing provisions of the Human Tissue Act 2004 apply to storage of tissue in England, Wales and Northern Ireland. There is no licensing scheme in Scotland.
- If the samples are from a research tissue bank (RTB) with ethical approval, please give the REC reference number for this approval if known. It is recommended that applications relating to use of tissue from approved RTBs are submitted to the same REC, which will be familiar with the circumstances in which the samples have been collected and the terms of any donor consent.

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Question 13 - Imported samples

- The Human Tissue Authority has issued a Code of Practice on the Import and Export of Human Bodies, Body Parts and Tissue, available at:

http://www.hta.gov.uk/guidance/codes_of_practice.cfm

- The REC will not undertake detailed review of the arrangements for collecting samples and obtaining consent in the exporting country. There is no need to provide copies of the informed consent documentation used. However, you should provide sufficient information to assure the REC that the collection of samples complies with legal, regulatory and ethical requirements in the exporting country, including appropriate ethical review.

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Question 14 - Storage of samples

- Review bodies will wish to know where the samples will be stored during the project and where tests and analysis will take place.
- Describe the arrangements for preserving the condition of the samples and for ensuring security and confidentiality of the samples and any linked data. Say who will be responsible for these arrangements and who will have access to the samples.

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Question 15 - Further storage or disposal of samples at the end of the project

- In England, Wales and Northern Ireland the storage of tissue for use in research requires a Licence from the Human Tissue Authority (HTA), unless the tissue is held for the purpose of a specific project with ethical approval or for which approval is pending.
- Ethical approval for storage of the samples would therefore be confined to the specific project described in this application form and the protocol. Applicants may seek approval for a project to be undertaken in several stages provided that these are clearly defined in the protocol and relate to the same set of research questions.

- The project-specific application form may not be used to seek open-ended approval for use of stored tissue in future research programmes (although the terms of the consent itself may be broad, allowing for future approved research using the same samples). Nor is it permitted to submit substantial amendments to approved projects in order to use tissue for another project with a different set of research questions.
- Where a researcher in England, Wales or Northern Ireland makes a specific project-based application but also plans to store the tissue beyond the life of the project for use in further projects, the following options are available:
 - At the end of the project the researcher could transfer the samples to a licensed research tissue bank (RTB) for further storage.
 - At the end of the project the researcher could transfer the samples to a licensed research tissue bank (RTB) for further storage.
 - At the end of the project, the researcher may make a further project-based application. The application must be submitted no later than the date on which the first project ends (as defined in the protocol), otherwise continued storage of the tissue would require a licence from the HTA.
 - The researcher may set up a new RTB and apply for a storage Licence from the HTA. Application may also be made for ethical review of the RTB, using the version of the application form designed for RTBs. The bank may seek "generic ethical approval" for a range of research projects to be carried out using the samples.
 - Applications may be made simultaneously at the outset for review of the project and the longer term RTB, using both application forms. The two forms should be submitted to the same REC and reviewed in conjunction. A storage licence will be required from the HTA at the end of the initial project.
- Detailed guidance on disposal is available in the HTA Code of Practice on the Removal, Storage and Disposal of Human Organs and Tissue (see http://www.hta.gov.uk/guidance/codes_of_practice.cfm).
- The researcher may continue to store the tissue without a Licence under the original REC approval only where this is essential as a record of the completed research project, for example to verify research data. Storage for this purpose without a Licence should continue for no longer than necessary.
- In Scotland, the licensing requirement does not apply and continued storage of samples by researchers after the end of the project may be lawful. However, for purposes of ethical review the same policy applies as in the rest of the UK. Ethical approval for specific projects is given for the duration of the project only. Continued storage for prospective research should be under appropriate controlled conditions as part of a managed tissue bank.

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Part B Section 5: New Samples

Question 1 - Type of human tissue or other biological material

- Describe the body sites involved and the format in which the samples will be supplied. Indicate if the samples are perishable in nature, their likely deterioration time and the purposes for which they will be used.

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Question 2 - Collection of samples

- Briefly describe the arrangements for collecting the samples, mentioning any involvement of collaborators. Where samples will be collected in a number of centres, indicate the type of health care professional who will be involved. You may cross-refer to information already provided in Part A of the form.

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Question 4 - Informed consent

- Where tissue is removed primarily for research purposes, informed consent is always required to remove, store and use the tissue.
- Where tissue is removed from the living primarily for diagnostic or therapeutic purposes (e.g. for a blood test or biopsy, or in the course of surgery), informed consent is always required for these purposes. However, under the Human Tissue Act 2004, any surplus tissue may then be lawfully stored and used in research without consent for this purpose provided that:
 - ◊ The research is ethically approved by a research ethics authority (i.e. a REC), and
 - ◊ The research is to be carried out in circumstances such that the researcher is not in possession, and not likely to come into possession, of information from which the donor can be identified.
- However, it is best practice to seek consent prospectively for use in research where possible. Consent for use in research may be added to the established consent procedure for routine diagnosis or surgical treatment.

- If consent is not to be sought for research, this should be ethically justified in your answer to Question A30-1.
- If consent is not to be sought for research, this should be ethically justified in your answer to Question A30-1.
- Where consent is to be sought, the answers to Questions A29 and A30-1 should describe how donors will be approached and who will undertake the consent process. The information sheet and consent form should be enclosed.
- It is accepted as good practice to seek "broad consent" to store and use tissue/data prospectively in a number of future projects, potentially in a range of research fields. The principle of broad consent has been endorsed in Parliamentary debates during the passage of the Human Tissue Act 2004 and in the HTA Code of Practice on Consent. It may not be possible to give donors specific information about the projects that will be carried out, but information sheets should give an indication of the types of research that might be conducted and the potential benefits.
- It is advisable to give donors specific information about the following potential uses of samples or data:
 - Export for use in research outside the UK
 - Animal research
 - Research involving human embryos and stem cells
 - Research into termination of pregnancy or contraception
 - Research involving genetic analysis
 - Commercial research.
- The informed consent process should also deal with:
 - Confidentiality of personal data
 - Whether donors would be able to withdraw consent and what the effect of this would be
 - The rights of donors in the event of financial gain from the results of research, and the "gifting" of samples.

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Question 5 - Samples from the deceased

- Under the Human Tissue Act 2004, "appropriate consent" is required to store or use tissue obtained from the deceased after 1 September 2006, unless the person died more than 100 years ago. Appropriate consent should be sought if not already been obtained for use in future research.
- Detailed guidance on consent to store and use tissue from the deceased is given in the Human Tissue Authority Code of Practice on Consent (available at http://www.hta.gov.uk/guidance/codes_of_practice.cfm).
- In the case of a deceased adult, appropriate consent means:
 1. The consent of the deceased person given before death.
 2. If there is no prior consent by the deceased person, the consent of a nominated representative.
 3. If no representative was appointed by the deceased person, a person in a qualifying relationship (see below).
- In the case of a deceased child, appropriate consent means:
 1. A person who had parental responsibility immediately before the child's death.
 2. If no person had parental responsibility, another person in a qualifying relationship.

Qualifying relationship

- Persons in a *qualifying relationship* are ranked in the following order:
 - (a) Spouse or partner (including civil partners)
 - (b) Parent or child
 - (c) Brother or sister
 - (d) Grandparent or grandchild
 - (e) Child of a brother or sister
 - (f) Stepfather or stepmother
 - (g) Half brother or half sister
 - (h) Friend of long standing.
- Where there is more than one person in the same rank in the hierarchy, the consent of any one of them will constitute appropriate consent.

- In the case of consent to analyse DNA or use the results of the analysis for research purposes, the consent of any person in the list above is enough – the list is unranked in this case.

Scotland

- Under the Human Tissue (Scotland) Act 2006, which was implemented on 1 September 2006, authorisation is required to use tissue from a deceased person for research purposes. Detailed guidance on the Act has been issued by the Scottish Executive in HDL(2006)46, which is available on the Scottish NHS website at:

http://www.sehd.scot.nhs.uk/mels/HDL2006_46.pdf

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Question 6 - Use of tissues or cells for human application

- Only answer Yes to this question if you will be using tissues or cells for human application in the research, e.g. transplantation.
- Guidance on use of tissues and cells for human application is available from the Human Tissue Authority at: http://www.hta.gov.uk/about_hta/eutcd_information.cfm.

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Question 7 - Licensing arrangements for research involving human application

- Detailed guidance on licensing issues is available from the Human Tissue Authority at: http://www.hta.gov.uk/about_hta/eutcd_information.cfm.
- Review bodies will wish to be assured either that licences are already in place or have been applied for, where this is necessary to comply with the EU Tissues and Cells Directive and the Human Tissue (Quality and Safety for Human Application) Regulations 2007.
- Please contact the HTA directly if expert advice is needed on licensing.

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Question 8 - Anonymisation of samples

- Samples will normally not be identifiable where obvious identifiers (e.g. name, address, date of birth) are removed at the point of release. However, consideration should be given to whether donors could be identifiable if viewed in conjunction with other publicly available information. This will depend on the information in the dataset and its rarity. For example, incidence of a rare disease in a woman aged 85 in a known postcode region might be identifiable to anyone with knowledge of the community or access to census data.
- Where surplus tissue from the living is to be used without specific consent for use in research, the samples must always be stored in either fully anonymised or linked anonymised form.

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Question 9 - Types of test or analysis

- Describe the methodologies to be applied to the study of the samples.
- Indicate the nature of the research data that will be generated by these methods.
- Highlight the types of analysis you anticipate may raise ethical questions and how you will deal with such issues.

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Question 10 - Analysis or use of genetic material

- Answer Yes to this question if the analyses may produce information that involves genetic sequence data, single nucleotide polymorphism data, genetic “finger print” data, ploidy data or cytogenetic data, including the detection of mutations or genetic variants.

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Question 11 - Findings of clinical significance

- Indicate whether the analyses described in question 10 could have prognostic, predictive or other significance for individual donors/subjects or their relatives.

- If so, describe the nature of the clinical significance for the individual subjects that might be encountered.

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Question 12 - Arrangements to notify individuals of clinically significant findings

- If No, indicate clearly the reasons why data will not be notified to the participants or their healthcare professionals. For example, the reasons may be based in ethics, practicality or science. Explain how the decision not to provide feedback to participants is consistent with the terms of their consent.
- If Yes, describe how the feedback will be provided – will it be directly to the participant or via a healthcare professional? In either case, please explain how the implications of the feedback will be explained to the participants and how they will be supported or counselled in light of the feedback. If some participants have indicated that they do not wish to receive feedback of clinical significance, how will you deal with this in the light of clinically significant information resulting from the research?

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Question 13 - Storage of samples

- Review bodies will wish to know where the samples will be stored during the project and where tests and analysis will take place.
- Describe the arrangements for preserving the condition of the samples and for ensuring security and confidentiality of the samples and any linked data. Say who will be responsible for these arrangements and who will have access to the samples.

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Question 14 - Further storage or disposal of samples at the end of the project

- In England, Wales and Northern Ireland the storage of tissue for use in research requires a Licence from the Human Tissue Authority (HTA), unless the tissue is held for the purpose of a specific project with ethical approval or for which approval is pending.

- Ethical approval for storage of the samples would therefore be confined to the specific project described in this application form and the protocol. Applicants may seek approval for a project to be undertaken in several stages provided that these are clearly defined in the protocol and relate to the same set of research questions.
- The project-specific application form may not be used to seek open-ended approval for use of stored tissue in future research programmes (although the terms of the consent itself may be broad, allowing for future approved research using the same samples). Nor is it permitted to submit substantial amendments to approved projects in order to use tissue for another project with a different set of research questions.
- Where a researcher in England, Wales or Northern Ireland makes a specific project-based application but also plans to store the tissue beyond the life of the project for use in further projects, the following options are available:
 - At the end of the project the researcher could transfer the samples to a licensed research tissue bank (RTB) for further storage.
 - At the end of the project, the researcher may make a further project-based application. The application must be submitted no later than the date on which the first project ends (as defined in the protocol), otherwise continued storage of the tissue would require a Licence from the HTA.
 - The researcher may set up a new RTB and apply for a storage Licence from the HTA. Application may also be made for ethical review of the RTB, using the version of the application form designed for RTBs. The bank may seek "generic ethical approval" for a range of research projects to be carried out using the samples.
 - Applications may be made simultaneously at the outset for review of the project and the longer term RTB, using both application forms. The two forms should be submitted to the same REC and reviewed in conjunction. A storage licence will be required from the HTA at the end of the initial project.
 - If none of the above steps are taken, the researcher would as a last resort need to arrange for disposal of the samples at the end of the project.
- Detailed guidance on disposal is available in the HTA Code of Practice on the Removal, Storage and Disposal of Human Organs and Tissue (see http://www.hta.gov.uk/guidance/codes_of_practice.cfm).
- The researcher may continue to store the tissue without a Licence under the original REC approval only where this is essential as a record of the completed research project, for example to verify research data. Storage for this purpose without a Licence should continue for no longer than necessary.
- In Scotland, the licensing requirement does not apply and continued storage of samples by researchers after the end of the project may be lawful. However, for purposes of ethical review the same policy applies as in the rest of the UK. Ethical approval for specific projects is given for the duration of the project only. Continued storage for prospective research

should be under appropriate controlled conditions as part of a managed tissue bank.

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Part B Section 8: CAG Information

Question 1 - HES data

- This refers to requests to the Health and Social Care Information Centre for a data extract from Hospital Episode Statistics (HES).

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Question 2 - Description of patient information

- This should be a brief general description of the information to be used.

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Question 6 - Justification for use of identifiable patient data

- Please provide justification for the use of identifiable patient data, including details of:
 - Evidence of independent support for the proposal;
 - The consequences of the activity not going ahead;
 - Why it is necessary to use identifiable patient data rather than anonymised or pseudonymised information, including details of;
 - What would be required for anonymised or pseudonymised data to be used to support this or similar purposes in the future;
 - The steps being taken to develop this as an option.
- The guidance available on the Health Research Authority (HRA) website in relation to reducing disclosure of confidential patient information should be reviewed at this stage. Please refer to the "Considerations and application guidance" at: <http://www.hra.nhs.uk/resources/confidentiality-advisory-group/>

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Question 11 - Classes of Section 251 support

- Indicate which type of section 251 support is sought (either Specific or Class support but not both) and, in the case of Class support, which Class(es) apply to this project.

Specific support

- Specific support provides support to an organisation to allow it to process data for a range of defined purposes, rather than on an individual study/project basis.
- Specific support requires Regulations to be laid before Parliament and would take over a year to implement. It is not therefore generally appropriate for research purposes.

Class support

- Class support provides support to a particular organisation to undertake a particular project.
- Please tick all classes that could apply.
- Class 6 should always be included as this provides permission for someone outside the clinical care team to have access to the confidential patient information in order to undertake the other classes.
- It should be noted that Section 251 only applies to medical purposes. These include preventative medicine, medical diagnosis, medical research, the provision of care and treatment, management of health and social care services. Classes 2 and 3 only apply to medical research.

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Question 12 - Compliance with the data protection principles

- Please note that while the question refers to the Data Protection Act 1998, you should complete this question to describe how your organisation satisfies the requirements of the Data Protection Act 2018 (DPA), including how you comply with the 6 Data Protection Principles. The on screen wording of the question and table for completion will be updated in due course.
- The 6 Data Protection Principles are:
 1. Processing should be lawful, fair and transparent (complete row 1 of the table)
 2. Purposes of processing should be specified, explicit and legitimate (row 2 of the table)
 3. Personal data should be adequate, relevant and not excessive (complete row 3 of the table)
 4. Personal data should be accurate and kept up to date (complete row 4 of the table)
 5. Personal data should be kept for no longer than is necessary (complete row 5 of the table)
 6. Personal data should be processed in a secure manner (complete row 7 of the table)
 Row 6 of the table may be left blank, however you should still complete row 8 of the table.
- For research the DPA 2018 provides exemption from some aspects of the Act. However where Section 251 support is in place, an exit strategy from the use of confidential patient data without consent should be identified.
- The Confidentiality Advisory Group (CAG) accepts that medical research is to be regarded as a purpose compatible to that for which the data was collected initially; hence the 2nd data protection principle is shaded out in the form.
- Section 251 support lifts the common law duty of confidentiality and allows disclosure of identifiable patient data without consent, but it does not set aside other aspects of the 1st data protection principle. Applicants should therefore demonstrate proposals to carry out fair processing, protection of the rights of data subjects and steps to anonymise or reduce the identifiability of data as soon as possible.
- There is therefore a requirement to make reasonable efforts to inform patients about how their information is used and seek their consent.
- If patients withhold or withdraw their consent for the use of their data this must be respected.

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Question 13 - Self-assessment

- More details about the Information Governance (IG) toolkit can be found at <https://www.igt.hscic.gov.uk>
- Instead of providing a system level security policy document, applicants to the Confidentiality Advisory Group (CAG) should provide a relevant IG Toolkit submission.
- Further information about this requirement can be found on the CAG resources page of the Health Research Authority (HRA) website at: <http://www.hra.nhs.uk/resources/confidentiality-advisory-group/>

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Question 14 - Information Guardian

- While compliance with legal requirements, including any obligations or restrictions imposed by Section 251, is the responsibility of everyone working within an organisation, a named individual is required to serve as the point of contact with the Confidentiality Advisory Group (CAG). In most circumstances, CAG would expect this person to be the head of the unit where the work will be carried out.
- It will be the responsibility of the Information Guardian to provide CAG, on request, with evidence that the organisation works within the conditions for processing identifiable patient data under the Data Protection Act (DPA) and Section 251.

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Question 16 - Other information

- Any information which you would rather remain confidential should be included in a separate supporting document clearly marked as in confidence.

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Part B: Section 9: Information Security

Question 2 - Measures to limit use of identifiable patient data

- The Confidentiality Advisory Group (CAG) will be unable to advise section 251 support to the Health Research Authority (HRA) for any application where there is insufficient evidence that identifiable patient data will be used only for the purposes described in the application, that access to the information is restricted, and that it is stored securely.
- Explain what steps have been taken to limit the use of, and access to, identifiable patient data, including details of how the use of identifiable patient data will be restricted to the purposes set out in your application.

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Question 3 - Compliance with information security standards

- Demonstrate that your organisation has adequate IM&T security and confidentiality standards. NHS organisations must confirm that they comply with the NHS security standards that include the ISO/IEC 27001 & 27002.
- Confirm that your organisation is committed to achieving the standards set out in ISO/IEC 27001& 27002, the Code of Practice for Information Security Management (2005).

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Question 5 - Data Protection Registration

- Provide details of Data Protection Registration/Notification. Applicants must supply a copy of their Data Protection Registration in order to confirm that they are registered for the purposes of analysis and classes of data described in the application.

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Part C: Research sites and investigators

Part C: Host organisations for research sites.

NHS Research Sites in England

If it is a Primary Care research site the host organisation will be one of the following:

- the LCRN geographic area in which the primary care site is located (Organisation look up 'Type' is LCRN AREA)
- the GP practice/independent contractor (Organisation look up 'Type' is PRACTICE)
- dentist (Organisation look up 'Type' is DENTIST)
- pharmacy (Organisation look up 'Type' is PHARMACY)
- optician. (Organisation look up 'Type' is OPTICIAN)

You will need to click the 'Organisation Search' button to enter information about the host organisation. In the Reference Data Organisation Search box please first select 'yes' to question "Is this a primary care research site?" and then use the search function to locate the appropriate host organisation. Select the 'copy data' link in the right hand column to enter the reference data into Part C.

For all other NHS participating organisations in England the host organisation is:

- the Trust;
- Care Trust; or
- Special Health Authority.

It may also be a Clinical Commissioning Group (CCG) but this should only be selected if the CCG is itself the research site.

You will need to click the 'Organisation Search' button to enter information about the host organisation. In the Reference Data Organisation Search box please first select 'no' to question "Is this a primary care research site?" and then use the search function to locate the appropriate host organisation. Select the 'copy data' link in the right hand column to enter the reference data into Part C.

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Create NHS SSI

Clicking this button will create an NHS Site Specific Information (SSI) form for this site. This NHS SSI form may be accessed from the 'Site Specific Forms' list towards the bottom left hand side of the Navigation Page.

Before you click this button please:

- Check whether you need to create an NHS SSI form for this site by referring to guidance about [applying for HRA Approval](#). In particular please refer to the sections about site level information for sites in England and, if applicable, the information for projects that have participating NHS/HSC organisations in Northern Ireland, Scotland and/or Wales.
- Ensure you complete all the fields in the row in Part C as the information you enter here will populate the form you create by clicking this button.

Projects including applications to ARSAC.

If in the project filter at question 4 you have selected applications to ARSAC then clicking the ‘Create NHS SSI Form’ button will simultaneously create both the NHS SSI form and the ARSAC Research Certificate Application (RCA) form for the site. Both forms will appear under the ‘Site Specific Forms’ list on the Navigation Page.

If you do not need an NHS SSI form for the site then you should use the separate ‘Create ARSAC RCA Form’ button as this will create the ARSAC RCA form for the site without an accompanying NHS SSI form.

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Create ARSAC RCA

Clicking this button will create an ARSAC Research Certificate Application (RCA) form for this site. This ARSAC RCA form may be accessed from the ‘Site Specific Forms’ list towards the bottom left hand side of the Navigation Page.

Before you click this button please:

- Check whether you need to create an NHS Site Specific Information (SSI) form for this site by referring to guidance about [applying for HRA Approval](#). In particular please refer to the sections about site level information for sites in England and, if applicable, the information for projects that have participating NHS/HSC organisations in Northern Ireland, Scotland and/or Wales. Note:
 - *If an NHS SSI form is not needed* then you will only need to create the ARSAC RCA form and you should proceed to use the ‘Create ARSAC RCA form’.
 - *If you need an NHS SSI Form and an ARSAC RCA form* for the site then you should use the ‘Create NHS SSI Form’ button instead of the ‘Create ARSAC RCA Form’ button as this will create both forms with a single click.
- Ensure you complete all the fields in the row in Part C as the information you enter here will populate the form you create by clicking this button.

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PART D: Declarations

D1 - Declaration by Chief Investigator

- Please read the bullet points carefully. By signing the declaration the CI is legally agreeing to its contents and will be personally liable for any deviation from this agreement.
- Before proceeding to submit IRAS application forms, please make sure you have correctly answered all questions in the Project Filter and all relevant sections and questions have been enabled and completed.
- Please ensure that all other relevant declarations in Part D are completed. You should then select the application you want to submit and follow the instructions under the Submission tab.
- Electronic authorisation is expected for most declarations in IRAS. Guidance is available under the Electronic Authorisation tab and on the Help page under Other Guidance.
- Where an ink signature is provided, you are advised to scan and save an electronic file of the signed page and to retain a copy of the signed application.

Publication of research summary

- Summaries of all studies submitted to RECs from 1 May 2008 are published on the Health Research Authority (HRA) website at <https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/>. Publication will take place no earlier than 3 months following the issue of the committee's final opinion (or the withdrawal of the application).
- Applicants should nominate a suitable contact point to be included in the summary. Contact details will only be included in the summary with explicit permission.
- Further information about publication of research summaries is available in the guidance on Question A6 in IRAS and at <https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/>.

Transfer of information

- It is Government policy to promote registration of research and public access to research findings affecting health and social care. Details from your application may therefore be transferred to other organisations involved in managing research and to publicly accessible registers.

Guidance last updated: 25 May 2018

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D1-1 - Declaration by Chief Investigator

- The Chief Investigator takes responsibility for ensuring that the information in Parts A-C of IRAS is complete and accurate
- Under Regulation 50 of the Medicines for Human Use (Clinical Trials) Regulations 2004 it is a criminal offence for any person to provide false or misleading information in making an application for an ethical opinion on a CTIMP or authorisation to conduct a clinical trial.

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The Data Protection Act 1998 was replaced by the Data Protection Act 2018 on 23 May 2018. As of this date, by signing this declaration you are agreeing that you understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.

Guidance last updated: 25 May 2018

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Publication of lay summary and ethical opinion

- Publication of the lay summary of the study (as provided in the application form) will be on the Health Research Authority (HRA) website (www.hra.nhs.uk) and will take place no earlier than 3 months following the issue of the committee's final opinion (or the withdrawal of the application). Publication of the lay summary is accompanied details of the Research Ethics Committee (REC) that reviewed the application and the opinion given by the REC as well as available reference numbers. This process has been in place since May 2008.
- The purpose of this is to ensure compliance with the Governance Arrangements for NHS Research Ethics Committees and the Clinical Trials Regulations; and support compliance with requirements under Freedom of Information (FOI) to publish information held by public bodies.
- Chief Investigators/Sponsors may apply to the REC for deferral of publication of the research

summary. Please note that where agreed this deferral applies to the research summary. It is not possible to defer publication of the opinion given by the REC.

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D2 - Declaration by the sponsor's representative

- The sponsor's declaration confirms an agreement in principle by the organisation(s) named in the application to act as sponsor(s) for the study.
- Final confirmation of sponsorship arrangements must be in place before the study starts.
- The person signing the declaration should be authorised by the sponsor organisation to do so. There is no requirement in the application for a particular level of seniority; the sponsor's rules about delegated authority should be adhered to.

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HRA Requirement to Register Clinical Trials as a Condition of REC Favourable Opinion

The HRA has reviewed this text to ensure greater consistency in the use of language in conveying standards that should be followed (ethical obligations or best practice) or must be followed (legal requirements) although readers are advised that the HRA holds both in high regard.

The HRA website material is a statement of the HRA understanding. Whilst the reader is encouraged to seek further clarification from the HRA in respect of any queries via the queries line, it will be for the reader to take their own legal advice as to what their legal duties are.

On 30 September 2013 registration of clinical trials in a publicly accessible database became a specific condition of the REC favourable opinion. The studies for which registration is required are the first four categories on the Integrated Research Application System (IRAS) filter question number 2, namely:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

For further information and detailed guidance about this requirement, including examples of accepted registers and the process for requesting deferral of registration, please refer to the Health Research Authority (HRA) website at: <http://www.hra.nhs.uk/resources/during-and-after-your-study/transparency-registration-and-publication/>

Sponsors should note: In order to fulfil its statutory responsibilities to promote transparency, the HRA has extended its audit activities on clinical trial registration from a compliance check on the requirements introduced in September 2013, to add an enquiry for all research in active recruitment in the UK, whether registration is legally required or expected as best practice.

The website link provides further information.

[This question specific guidance was last updated on 19 August 2015]

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Publication of lay summary and ethical opinion

- Publication of the lay summary of the study (as provided in the application form) will be on the Health Research Authority (HRA) website (www.hra.nhs.uk) and will take place no earlier than 3 months following the issue of the committee's final opinion (or the withdrawal of the application). Publication of the lay summary is accompanied details of the Research Ethics Committee (REC) that reviewed the application and the opinion given by the REC as well as available reference numbers. This process has been in place since May 2008.
- The purpose of this is to ensure compliance with the Governance Arrangements for NHS Research Ethics Committees and the Clinical Trials Regulations; and support compliance with requirements under Freedom of Information (FOI) to publish information held by public bodies.
- Chief Investigators/Sponsors may apply to the REC for deferral of publication of the research summary. Please note that where agreed this deferral applies to the research summary. It is not possible to defer publication of the opinion given by the REC.

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D3 - Declaration for student projects by academic supervisor

- This declaration should be completed by the academic supervisor for all student applications.
- Academic supervisors should note that tasks under the responsibility of the academic supervisor may be delegated to the clinical supervisor at the site where research activity is

undertaken. Any such arrangement with a clinical supervisor should be agreed with the research site.

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D4 - Declaration by the Information Guardian

- This declaration applies only to applications to the Confidentiality Advisory Group (CAG).
- While compliance with legal requirements, including any obligations or restrictions imposed by Section 251 support, is the responsibility of everyone working within an organisation, a named individual is required to serve as the point of contact with CAG. In most circumstances, CAG would expect this person to be the head of the unit where the work will be carried out.
- It will be the responsibility of the Information Guardian to provide CAG, on request, with evidence that the organisation works within the conditions for processing identifiable patient data provided under the Data Protection Act 1998 and Section 251 of the Health and Social Care Act 2001.

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