

Ethical review of research databases

1. IRAS contains for the first time a specific application form for ethical review of a research database. This note sets out interim guidance for NHS /HSC Research Ethics Committees on policy and procedures for review of database applications.
2. This guidance is issued pending the next revision of the NRES Standard Operating Procedures. Version 5.0 of the SOPs (due for release in April 2010) will include procedures for research database applications. The model approval conditions for research databases are already included in the SOPs at Annex L.

Research databases

3. Organisations responsible for the management of research databases anywhere in the UK may apply for ethical review of their arrangements for collection, storage and use of data, including arrangements for release of anonymised or pseudonymised data to external researchers.
4. In this context, a “research database” means a collection of personal data on human subjects for use in research, i.e. for analysis. The research database form is not intended to apply to research registers, research management databases or databases of potential participants in research such as those held by Phase 1 trial companies.
5. In the IRAS Project Filter, on-line guidance defines a research database as:

A collection of data, which is stored for potential research use beyond the life of a specific project with ethical approval or for which ethical approval is pending.
6. Where an establishment holds both human biological material (including DNA) and data for analysis, it should apply using the Research Tissue Bank (RTB) application form rather than the Research Database form.

Application for ethical review is voluntary

7. There is no formal requirement for research databases to apply for ethical review under NHS research governance systems, and ethical and other approvals¹ would only be required by legislation if processing identifiable data without consent. Applications for ethical review will therefore normally be made on a voluntary basis.
8. However, ethical approval for a database may have benefits by facilitating programmes of research using data on human subjects without a need for individual project-based ethical approval. The database application form has an option for the applicant to seek generic ethical approval, subject to conditions agreed with the REC (see paragraphs 16-20 below).

¹ Approval under Section 251 of the NHS Act 2006 (previously Section 60 of the Health and Social Care Act 2001) is required from the National Information Governance Board's Ethics and Confidentiality Committee to process identifiable data of patients receiving treatment in England and Wales without consent (see paragraphs 23-26)..

Booking applications

9. Applications for ethical review of research databases should normally be booked for review via the Central Allocation System (CAS). Applications will be allocated by CAS to a flagged REC. The current list of flagged RECs for database applications is as follows:
 1. Cambridgeshire 2 Research Ethics Committee
 2. Health and Social Care Research Ethics Committee 2 (Northern Ireland HSC REC 2)
 3. Newcastle and North Tyneside Research Ethics Committee 1
 4. North West 5 Research Ethics Committee – Haydock Park
 5. Oxfordshire Research Ethics Committee C
 6. South East Research Ethics Committee
 7. South West 3 Research Ethics Committee
 8. Trent Research Ethics Committee
10. Lists of flagged RECs are kept under review by the NRES Operations Team and may be revised from time to time. The latest information is available on the NRES website by using the advanced search option at <http://www.nres.npsa.nhs.uk/contacts/find-your-local-rec/>.
11. Although booking via CAS with a flagged REC is strongly recommended, applicants may opt to apply to another committee within their geographical domain if they prefer.

Validation

12. Applications should be regarded as valid if all the following criteria are satisfied:
 - (a) The IRAS application form for ethical review of a research database has been submitted in typescript.
 - (b) The applicant's checklist in IRAS has been submitted (see Annex A to this guidance).
 - (c) All relevant sections and questions have been completed and submitted. All documents listed in the checklist have been submitted.
 - (d) The application form has been signed by the applicant. *(Note: It is planned to add a requirement for signature by the "Data Controller" in future. The Data Controller is the person with overall responsibility for management and oversight of the Database, including compliance with conditions of REC approval.)*
 - (e) A protocol or other document describing arrangements for management of the database has been submitted.
 - (f) Where consent is to be sought from data subjects, copies of all information sheets and consent forms have been enclosed.

- (g) All supporting documents have been marked with version numbers and dates.
- (h) The applicant is based within the United Kingdom.

Process of ethical review

- 13. The process of ethical review is the same as for project-based applications. All references to the Chief Investigator in Sections 2 and 3 of the SOPs should be read as applying to the person submitting the application.
- 14. Where an unfavourable opinion is issued, the usual options for further ethical review described in Section 7 of SOPs apply.
- 15. Substantial amendments to the terms of ethical approval for a database should be reviewed under the procedures in Section 5 of SOPs in the same way as substantial amendments to specific research projects. The NRES Notice of Substantial Amendment form can be completed in IRAS for applications made initially in IRAS.

Conditions of ethical approval

- 16. Applicants may seek generic ethical approval for future projects undertaken using data from the database, in the same way as for Research Tissue Banks.
- 17. The terms of this approval will normally cover both:

- (i) *Approval for the Research Database team*

The research team managing the Research Database (“the Research Database team”) will normally have consent from data subjects to process their personal data. The terms of the generic approval will therefore permit the Research Database to collect, store and use identifiable data for the purposes for which consent has been sought. These should be described in the REC application and will typically include activities such as data cleansing, linkage, anonymisation / pseudonymisation, audit and verification, as well as analysis in research studies conducted by researchers within the team. All of these activities will be conducted with consent, unless exceptionally approval from the National Information Governance Board (NIGB) is obtained to process identifiable data without consent (see paragraphs 23-26).

The Research Database must have policies in place to ensure the continued security of the data, to minimise access to identifiable data within the Research Database team and ensure that duties of confidentiality are enforced. The REC should expect to receive suitable assurances about these policies in the application.

- (ii) *Approval for external researchers receiving anonymised data*

Research Databases may also have policies for giving access to external researchers able to derive useful studies from the data. In this context, “external researchers” means researchers outside the Research Database team. They may be within the wider organisation (e.g. in another department

of the establishment responsible for the Database) or in other organisations. These projects will generally not have consent to process personal data unless they are established collaborations and have been specifically covered in the terms of consent (in this case, they may be considered part of the Research Database team). Therefore data can normally only be released in effectively anonymised or pseudonymised form. If external researchers require access to identifiable data to undertake a study, this would require further consent and ethical review.

Data sharing is encouraged in the interests of maximising the research potential of stored data, provided that adequate safeguards are in place to protect confidentiality. The REC may give generic approval extending to studies by external researchers subject to conditions. The Research Database team must have clear policies in place for making decisions on access and processes for effectively anonymising data extracts prior to release. Data Sharing Agreements should be in place with researchers.

18. Generic approval may be given for a period of up to 5 years and will be renewable.
19. Where generic approval is given, researchers would not need to make further project-specific applications, provided their research is within the terms of the approval conditions issued by the REC. *In particular, external researchers relying on generic approval must not receive data in identifiable form or be able to identify subjects through linkage with other databases.* Where access to identifiable data or further contact with data subjects is proposed, external researchers should submit their own project-specific applications to the REC.
20. Model approval conditions (SL-AC4) are attached at Annex B to this guidance. They are also included at Annex L to the NRES SOPs. This template should be used by flagged RECs and other RECs reviewing database applications. The REC has discretion to modify the conditions or attach further conditions appropriate to the application. The template will be available in RED in due course.

Summary of issues for ethical review

21. Detailed guidance on the management of research databases is in preparation. This will be published on the NRES website as soon as it is available. In addition, question-specific guidance on the application form will be made available in IRAS. This will provide both applicants and RECs with information about the key issues to be addressed in application and ethical review.
22. In the interim, RECs may find it helpful to note the following summary of the main issues to be considered in applications:
 - Roles and responsibilities for management and oversight of the Database
 - Types of data to be collected; what personal identifiers or particularly sensitive information will be held?
 - What types of research will be supported by the Database, what are the potential benefits?
 - Arrangements for data collection and consent from data subjects; information sheets and consent forms; policy on withdrawal of consent

- Engagement with patients and public, policy on publication of research findings
- Database Security policy
- Access to identifiable data within the Research Database team and confidentiality policies
- Applications from external researchers, how decisions on access are made
- Processes for effective anonymisation or pseudonymisation of data extracts prior to release
- Conditions of data sharing agreements with external researchers, in particular no attempt to re-identify data subjects through linkage with other databases and no onward disclosure to third parties.

Applications to the National Information Governance Board

23. The common law duty of confidentiality owed by health professionals in regard to information provided by patients in the course of clinical care, and the principles of the Data Protection Act 1998, apply to the processing of data by Research Databases in the same way as to specific research projects. Consent to access health records and/or process identifiable data for research must be sought, unless exceptionally approval is obtained from the National Information Governance Board (NIGB) for England and Wales to set aside the normal duty of confidentiality for medical purposes. Such applications are reviewed by the NIGB's Ethics and Confidentiality Committee (ECC)
24. Research Databases in England and Wales may sometimes apply to the ECC in parallel with the REC application. Essentially there are two types of application that ECC will consider in relation to research databases:
 - Application for individuals outside the clinical care team to access patient records to identify cohorts, with the intention of then approaching the data subjects to seek their consent for personal data to be held and processed by the Research Database team.
 - Application to use personal data in research without consent. NIGB ECC approval for this purpose is likely to be only in exceptional circumstances but may be considered particularly for historic datasets where it would not be feasible or appropriate to contact data subjects for consent. To obtain approval, applicants need to define the uses of the data, demonstrate the potential benefits of the research, and say why it could not be done as effectively using anonymised data or by collecting new data prospectively with consent.
25. Detailed guidance on the role of ECC and guidance for applicants is available at: <http://www.nigb.nhs.uk/ecc>.
26. NRES and NIGB are in discussion about arrangements for communication between RECs and ECC where applications are made in parallel. Agreed guidance will be published in due course. In the interim, RECs are encouraged to communicate directly with the ECC Secretariat where expert advice is required on proposals to use personal data without consent, or to discuss ethical concerns. The operational manager should be made aware of

the discussions. Contact details for the Secretariat are available via the weblink above.

SSA exemption

27. All research database applications are SSA-exempt. The ethical review applies to the management of the database as a whole, including arrangements made with collaborators for collection, storage or use of data.
28. Part C of the IRAS application form should list all Data Collection Centres (DCCs), i.e. collaborating centres who provide data under the terms of a supply agreement between their organisation and the database. DCCs are not regarded as research sites for the purpose of the Research Governance Framework.

NHS management permission

29. Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.
30. Research permission is also not required by collaborators at DCCs as these are not regarded as research sites.
31. The Research Database team is advised to provide NHS R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.
32. NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval. Where the data is received in non-identifiable form and the research is covered by the terms of generic ethical approval for the database, no further REC application is required but the database should list the project in its annual report to the REC.

Use of RED

33. RED allows Co-ordinators to register research databases as a specific application type. Standard letters have been slightly amended to use the appropriate terminology. The model approval conditions are available in RED.

Further advice

34. Requests for further advice on database applications should be made via operational management in the usual way.

35. Any comments from RECs on the policy for ethical review or the model approval conditions may be sent direct to David Neal, NRES Deputy Director (Policy), at david.neal@nres.npsa.nhs.uk.

National Research Ethics Service
National Patient Safety Agency

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CONDITIONS OF ETHICAL APPROVAL

Research Ethics Committee:	
Research Database:	
Data Controller:	
Establishment:	
REC reference number:	
Name of applicant:	
Date of approval:	

Ethical approval is given to the Research Database team (“Database team”) based within the Establishment by the Research Ethics Committee (“the Committee”) subject to the following conditions.

1. Further communications with the Committee
 - 1.1 Further communications with the Committee are the personal responsibility of the applicant.

2. Duration of approval
 - 2.1 Approval is given for a period of 5 years, which may be renewed on consideration of a new application by the Committee, taking account of developments in legislation, policy and guidance in the interim. New applications should include relevant changes of policy or practice made by the establishment since the original approval together with any proposed new developments.

3. Generic approval for the Research Database team
 - 3.1 Ethical approval is given for processing of personal data by the Research Database team for the purposes described in the application. This includes specific research projects undertaken by the Database team using the data, subject to the following conditions:
 - 3.1.1 The research project is within the fields of health or social care research described in the application.
 - 3.1.2 The research protocol has been subject to scientific critique, is appropriately designed in relation to its objectives and (with the exception of student research below doctoral level) is likely to add something useful to existing knowledge.
 - 3.1.3 The processing of the data will comply with the terms of informed consent from data subjects.
 - 3.2 Any research project requiring researchers to undertake additional procedures involving subjects, other than data collection arrangements described in the application, is not covered by generic approval for the Database. Additional research procedures should be the subject of further ethical review, either as a substantial amendment to the terms of generic approval for the Database, or separate application for ethical review of a specific project.
 - 3.3 A Notice of Substantial Amendment form should be submitted to seek the Committee's agreement to change the conditions of generic approval for the Database.

[Select Option A or B as appropriate]

[Option A: For Databases receiving generic approval on behalf of external research outwith the Research Database team]

4. Generic approval for external researchers
 - 4.1 Data may be supplied and used in research projects to be conducted by researchers and research institutions outwith the Research Database team within the UK *[and in other countries]* in accordance with the following conditions.
 - 4.1.1 The research project is within the fields of health or social care research described in the approved application form.
 - 4.1.2 The Research Database team should be satisfied that the research has been subject to scientific critique, is appropriately designed in relation to its objectives and (with the exception of student research below doctoral level) is likely to add something useful to existing knowledge.
 - 4.1.3 Research must be conducted in circumstances such that data subjects are not identifiable to the external researchers. Data must be effectively anonymised or pseudonymised prior to release to external researchers. The researchers should undertake to treat datasets in

confidence and not to attempt re-identification of data subjects through linkage with other datasets.

- 4.1.4 A data sharing agreement must be in place with all external researchers to ensure processing of the data in accordance with the terms of the ethical approval and any other conditions required by the Research Database team.
- 4.2 A research project using data from the Database in accordance with these conditions will be considered to have ethical approval from the Committee under the terms of this approval.
- 4.3 Any research project requiring external researchers to be able to identify data subjects for purposes of linkage with other datasets, or in order to collect further data from subjects or their care records or undertake other research procedures involving subjects, is not covered by this approval. Such projects should be the subject of further project-specific application for ethical review.
- 4.4 The Research Database team may require any researcher to seek specific ethical approval for their project. Such applications should normally be made to the Committee.

[Option B: For Databases where the applicant has not applied for generic ethical approval for external researchers, or such approval has not been given by the Committee]

4. Projects conducted by external researchers

- 4.1 The approval for the Database does not confer ethical approval for research projects conducted by external researchers using data from the Database. Where ethical approval is required under research governance arrangements, a specific application should be made by the researcher. Such applications should normally be made to the Committee.
- 4.2 To request generic ethical approval for external researchers, the applicant should submit a new application rather than a Notice of Substantial Amendment.

5. Records

- 5.1 The establishment should maintain a record of all internal and external research projects using data from the Database. The record should contain at least the full title of the project, a summary of its purpose, the name of the Chief Investigator, the sponsor, the location of the research, the date on which the project was approved by the establishment, a brief summary of the dataset released (including any sensitive data), whether the data was accessed by the researcher in identifiable form, and any relevant reference numbers. For external research, the record should indicate whether data has been released under the terms of the generic approval for the Database or for a project with specific ethical approval.
- 5.2 The establishment should maintain a risk register and a record of any serious adverse events (see also paragraph 7.1).

- 5.3 The Committee may request access to these records at any time.
- 5.4 The Research Database team should maintain a publicly accessible register of research projects using data from the Database.
6. Annual reports
- 6.1 An annual report should be provided to the Committee listing all projects for which data has been released in the previous year. The list should give the full title of each project, the name of the Chief Investigator, the sponsor, the location of the research and the date of approval by the establishment. The report is due on the anniversary of the date on which ethical approval for the Database was given.
- 6.2 The Committee may request additional reports on the management of the Database at any time.
7. Substantial amendments
- 7.1 Substantial amendments should be notified to the Committee and ethical approval sought before implementing the amendment. A substantial amendment generally means any significant change to the arrangements for the management of the Database as described in the application to the Committee and supporting documentation.
- 7.2 The NRES Notice of Substantial Amendment form should be used to seek approval. The form should be completed in the Integrated Research Application System.
- 7.3 The following changes should always be notified as substantial amendments:
- 7.3.1 Any significant change to the policy for use of the data in research, including changes to the types of research to be undertaken or supported by the establishment.
 - 7.3.2 Any significant change to the types of data to be collected and stored, or the circumstances of collection.
 - 7.3.3 Any significant change to informed consent arrangements, including new/modified information sheets and consent forms.
 - 7.3.4 Any proposed change to the conditions of approval
 - 7.3.5 Any other significant change to the location, management or governance of the Database.

8. Serious adverse events
 - 8.1 The Committee should be notified as soon as possible of any serious adverse event or reaction, any serious breach of security or confidentiality, or any other incident that could undermine public confidence in the ethical management of the data.

9. Changes in responsibility
 - 9.1 The Committee should be notified of any change in the contact details for the applicant or where the applicant hands over responsibility for communication with the Committee to another person at the establishment.

10. Closure of the Database
 - 10.1 Any plans to close the Database should be notified to the Committee as early as possible and at least two months before closure. The Committee should be informed of the arrangements to be made for destruction of the data or transfer to another research database or archive, and of the arrangements to notify data subjects where appropriate.
 - 10.2 Where data is transferred to another research database (“the second database”) or archive, the ethical approval for the Database is not transferable. Where the second database is ethically approved, it should notify the responsible Research Ethics Committee. The terms of its own ethical approval would apply to any data it receives. If the second database is not ethically approved, the responsible establishment may seek ethical approval by submitting a new application to the Committee.
 - 10.3 Where data is transferred to another research database, any projects already underway using data supplied from the Database in accordance with these conditions continue to have ethical approval for the duration of those projects.

11. Compliance with approval conditions
 - 11.1 Oversight mechanisms should be in place to ensure these approval conditions are complied with. Compliance is the personal responsibility of the Data Controller.
 - 11.2 The Committee should be notified as soon as possible of any breach of these conditions.
 - 11.3 Where serious breaches occur, the Committee may review its ethical approval and may, exceptionally, suspend or terminate the approval.