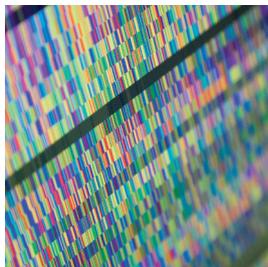
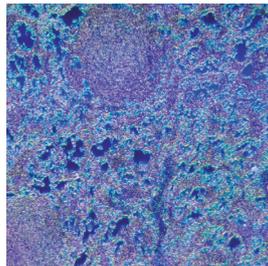
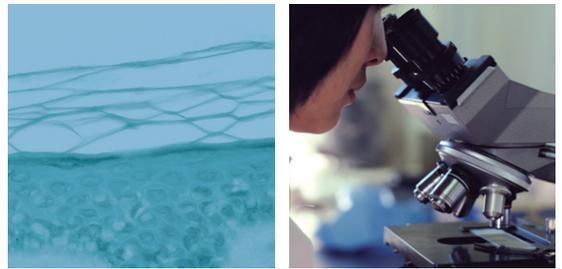


MRC ethics series

Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines



Foreword

The Medical Research Council (MRC) is dedicated to improving human health through excellent medical research, and expects the research it supports to be conducted according to the highest achievable ethical standards.

Samples of human biological material are used for many purposes and are of increasing importance as the MRC and other research funders, whether public, charitable or commercial, prioritise areas which rely upon access to human biological samples. Such areas include:

- Stratification of diseases;
- Understanding disease pathways and mechanisms in humans (experimental medicine); and
- Reduction of animal use by replacement with human models of disease, for example by creating pharmacodynamic models from human biological material samples.

Since the publication of the original guidance in 2001, there has been a strengthened MRC and cross-funder commitment to ensuring that research resources (biosamples and data) are supported with multiple use in mind, are discoverable and widely accessible. A number of changes to the legislative and regulatory landscape regarding research involving human biological material have taken place, and there has been a shift in public attitudes towards this type of research, encouraging a high level of transparency in the collection, storage and use of samples.

This document is part of the MRC's Ethics Series and sets out the MRC's expectations for MRC Units and Institutes, MRC University Units, MRC Centres and MRC grant holders in the form of principles, guidelines and standards to foster good research practice in all MRC-funded research. Additional advice and specific expectations for MRC Institutes and Units is provided in Annex 1. While this document is primarily for those involved in research supported, in whole or in part, by the MRC, we hope it will also be useful to others, including those involved in teaching and training of researchers and pathologists.

It is designed to be a 'living' document i.e. it will be based on the MRC website and the links and content updated as and when required. It is also supported by a series of Human Tissue Legislation Summaries, developed by the MRC Regulatory Support Centre (RSC)*.

* MRC RSC Human Tissue Legislation Summaries
<https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/human-tissue/>

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Introduction

The ethical use of human biological samples (see Glossary for definition) is in the interests of participants, researchers and society. Researchers should ensure the wishes and interests of the donor, where known, are respected at all times and the welfare of research participants should always take precedence over the interests of science and society.

The MRC expects its funded researchers to adhere to the highest ethical standards in medical research and to conform to requirements and guidance set out in this document and by national and international regulatory bodies, professional bodies, and local research ethics and governance frameworks. This document aims to clarify these expectations and how they apply within MRC Units, Institutes, University Units and Centres and to MRC funded grants, fellowships and studentships. It focuses on high-level ethical principles and provides more detailed guidance to ensure these principles can be achieved in practice.

This guidance relates to research purposes only and excludes clinical diagnostic purposes, clinical audit, service evaluation, disease surveillance or quality control of existing diagnostic testing procedures¹.

This document is not intended to reiterate the legal requirements relating to storage and use of human biological material in the UK, these can be found in the MRC Regulatory Support Centre Human Tissue Legislation Summaries². Researchers should be aware of all legal requirements pertaining to their area of research and keep up to date with any relevant changes. The MRC Regulatory Support Centre has also developed e-learning modules and other resources intended to support and guide researchers working with human biological material³.

The principles and guidelines outlined in this document are intended to complement statutory or regulatory requirements, codes of conduct and ethical standards relating to specific professions, research areas or settings, or the guidelines of other research funders. Local organisational policies and procedures, and relevant MRC policies and position statements, including those within the MRC's Ethics Series⁴, should also be considered.

References and related links

1. Health Research Authority's: Is my study research
<http://www.hra-decisiontools.org.uk/research/>
2. MRC Regulatory Support Centre: Human Tissue Legislation Summaries
<https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/human-tissue/>
3. MRC Regulatory Support Centre website <https://mrc.ukri.org/regulatorysupportcentre>
4. MRC website: Research policy and ethics <https://mrc.ukri.org/research/policies-and-guidance-for-researchers/>

1. Principles

The following principles outline the MRC's expectations relating to the conduct of research involving human biological material. They should underpin all MRC-funded research within the MRC's own research units and institutes and in other research organisations whether they are supported either in whole, or in part, by the MRC.

Samples of human biological material should be treated as donations* and research involving these samples should be conducted with respect and transparency. The human body and its parts should be treated with respect, and before approaching potential donors, researchers should be aware there may be individual, cultural or religious differences in the meaning and significance attached to the body or specific parts of it. Researchers should aim to achieve an environment of trust and respect with participants, recognising the altruism of providing samples for use. This environment can be fostered by maintaining a high level of transparency in every area of research practice e.g. from consent to the potential future use of samples, and dissemination of research results.

Research should only go ahead if the potential benefits outweigh any potential risks to the donors of the samples. The physical risks involved in donating samples for research will usually be minimal, but the risk that information from laboratory tests or linked data of a sample might harm the donor or their interests must not be forgotten.

Maximise the research use of collections of samples to benefit science and society – both by planning for the futures uses of new collections, and fully using existing collections. Wherever possible, researchers should make use of existing resources in an ethical manner with respect and transparency for the donors, rather than collecting new samples. Awareness and use can be improved through high quality online information about the resources. New and existing collections of samples can be made more useful by choice of sample preparation and storage techniques; ensuring better characterisation of samples, increasing linkage to accurate clinical data, and obtaining broad and enduring consent where possible¹. Samples should not be stored unused for long periods of time or destroyed unnecessarily.

There may be research results with health relevance that individual participants could be made aware of. Researchers must decide at the outset what their strategy will be regarding feedback of health related findings. Detailed guidance is available in the Wellcome Trust / MRC Framework on the feedback of health related findings in research².

The human body and its parts shall not, as such, give rise to direct financial gain. Researchers may not sell for profit samples of human biological material they have collected as part of MRC funded research, and research participants should never be offered any financial inducement to donate samples. Payment of reasonable expenses or costs is, however, acceptable³. Donors should be informed if their samples might be used in commercial research. Intellectual property (IP) rights arising from research using human biological samples may be sold or licensed in the same way as other IP rights.

Whenever seeking consent to collect and use samples for research, the information provided to potential donors should be understandable and supportive of the participant in making the decision to donate or not. Consent is one route of delivering transparency and fostering trust between the researcher and participant. When seeking consent, it should be sought from a person who is both appropriately informed and competent to make the decision to participate or not (or from an appropriate person on their behalf if the potential donor lacks this capacity)⁴. When obtaining consent, it is prudent to consider the value of those samples for future research. Broad and enduring consent (also referred to as generic consent) to include storage and use for future research should be sought whenever possible.

* Donated samples are often described as 'gifts' although it is recognised that donors of samples are not usually regarded as having ownership or property rights in these.

Patients should be informed when material left over following diagnosis or treatment (described as surplus to clinical requirements) might be used for research. Samples collected during routine diagnostic procedures are an extremely valuable potential resource for researchers. The research use of diagnostic/pathology archives without consent in place is permitted in law in certain circumstances⁵ and is viewed as ethical in these circumstances by the MRC. Engaging the public on the potential benefits and governance of use of surplus material for research will improve transparency and trust between donors and researchers. It is good practice to consider obtaining separate consent for the storage and use of such surplus material for research purposes wherever possible; where this is not reasonably possible appropriate information should be provided so that patients are aware of the potential use of such samples.

Research involving human biological material should undergo independent ethical review (with very limited exceptions). This ensures the rights, safety, dignity and well-being of research participants are safeguarded and, where applicable, legal requirements in tissue legislation are met. This review is normally carried out by a Research Ethics Committee (REC) within the NHS or a University.

Researchers should treat all personal and medical information relating to research participants as confidential. The value of samples of human biological material can be maximised by maintaining links with associated personal or clinical data relating to the donor. People who donate samples for research must be told what personal or medical information about them will be used in the research, who it might be shared with, and what safeguards are in place to protect their confidentiality. This applies as much to the results of laboratory tests done as part of the research project as to information obtained directly from donors or from their medical records⁶. Where genetic research is being conducted, greater explanation may be necessary, for example of the potential implications for other family members.

The ethical and legal principles guiding the use of personal information in research is detailed in the MRC Ethics Series guidance 'Personal information in medical research'⁶. More information is also provided in the General Medical Council guidelines on confidentiality⁷, and the MRC Regulatory Support Centre free e-learning module on 'Research Data and Confidentiality'⁸.

Researchers should be aware of, and keep up to date with, all ethical, legislative, regulatory and governance requirements relating to their area of research. This includes working with teams and individuals within relevant organisations who have a corporate responsibility to ensure that these requirements are met⁹.

References and related links

1. UK Research Funders Vision for Human Tissue Resources (2010/11)
<http://www.ukrcr.org/wp-content/uploads/2014/03/Vision+for+human+tissue+resources.pdf>
2. Medical Research Council/Wellcome Trust: Framework on the feedback of health-related findings in research (2014)
<https://mrc.ukri.org/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf>
3. Nuffield Council on Bioethics: Human Bodies: Donation for medicine and research (2011)
http://nuffieldbioethics.org/wp-content/uploads/2014/07/Donation_full_report.pdf
4. Human Tissue Authority (HTA) Codes of Practice: Code A: Guiding principles and the fundamental principle of consent <https://www.hta.gov.uk/hta-codes-practice-and-standards-0>
5. MRC Regulatory Support Centre: Human Tissue Legislation Summaries: Consent
<https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/human-tissue/>
6. MRC Ethics Series: Using information about people in health research (2016/17)
<http://www.highlights.rsc.mrc.ac.uk/PIHR/index.html>
7. General Medical Council: Guidelines on Confidentiality (2009)
http://www.gmc-uk.org/guidance/ethical_guidance/confidentiality.asp
8. MRC Regulatory Support Centre (RSC): Research, GDPR and confidentiality: what you need to know (2018)
<https://byglearning.co.uk/mrcrsc-lms/course/index.php?categoryid=1>
9. MRC Ethics Series: Good Research Practice
<https://mrc.ukri.org/research/policies-and-guidance-for-researchers/good-research-practice/>

2. Ownership, custodianship and the gift relationship

Legally and ethically, a researcher cannot own a human body (or a sample of that human body, once it has been removed from the donor). Rather the MRC considers their role is as a custodian of that sample taking on certain responsibilities as part of that role. The custodian is responsible for the safekeeping of samples, control of the use of samples, transfer to third parties (if applicable) and eventual disposal (if required), all in accordance with legislation and the expectations of the donor. The issue of ownership rights over human biological material is discussed in more detail elsewhere¹.

It is important to note that although researchers do not originally own the sample itself, they can come to 'own' the product of work or skill applied to that sample. This may involve intellectual property (IP) rights generated from a sample. Patenting of inventions based on, or using, biological material of human origin is covered by the EU Directive on the Legal Protection of Biotechnological Inventions².

The MRC requires that samples of human biological material donated for research are treated as donations, although there will sometimes be conditions attached. In this way, a 'gift relationship' between research donors and researchers can be promoted, highlighting the altruistic motivation for participating in research. It is important that the participant understands and agrees to the proposed use(s) of the donated material where this is known, and what would happen to any IP rights generated from the donated sample, to avoid any uncertainty or detriment to the participant. Participants must be clear who will be responsible for custodianship of the sample and control of any personal or confidential data related to it (and under what circumstances custodianship can be transferred to a third party if applicable).

While an individual may have day-to-day responsibility for management of a collection of human biological material, the MRC considers that it is more appropriate for formal responsibility for custodianship of collections of human material to rest with institutions/corporate bodies rather than with individual researchers. This could be for example through the Licence Holder in Human Tissue Authority (HTA) licensed establishments or the accredited Health Board in Scotland. This provides greater security for collections, better assurance that donors' rights will be protected and makes it easier to deal with changes in individual circumstances of the research team. The University, hospital or other host institution where the researchers are based (or the HTA licensed establishment / accredited Health Board in Scotland) will usually be the most appropriate body to have formal responsibility for custodianship of human material donated for research, but occasionally the MRC will wish to retain custodianship of collections that it funds. The MRC understands that custodianship brings with it the right to determine what happens to a collection after the original project funding is finished in line with donors' expectations, and also the responsibility for subsequent maintenance.

For all new collections of human biological material funded by the MRC, researchers and their host institutions must reach agreement with the MRC on specific arrangements for the custodianship and control of use of sample collections (both while the project is ongoing and after it is finished) before funding is released. It is expected that samples collected with public monies will be fully utilised for research, and so arrangements for maintenance and access, including by other research groups, following the initial funded project should be made. The MRC may rarely wish to consider having formal responsibility for custodianship of the collection. For many old collections, no specific arrangements for custodianship of samples and management of access will have been put in place. This can present problems when researchers retire or move to a different job, or when there is disagreement over who should be allowed to use the samples. When a researcher wishes to move samples to a new location, the agreement of the current and the future host institution must be sought, and contributing organisations must be consulted where possible. The terms of the original consent and ethics approval should be reviewed, and amendment sought if necessary. When a researcher leaves an

organisation and sample collections are to be retained, the institution should ensure arrangements are put in place for future maintenance and management, and that a new person is identified to take on responsibility for the collection.

It is good practice to offer research participants the opportunity to be kept informed about the general results of research projects completed using the samples they have donated, though this may not be appropriate or possible in all circumstances. Such communication with participants acknowledges their contribution, shows respect and supports transparency in research. Participants could be informed by posting information on research outcomes on a website, or by offering them the opportunity to receive a newsletter. When new predictive tests of clinical value become available as a result of the research, where possible participants could be informed how to access these tests if they wish.

References and related links

1. Nuffield Council on Bioethics: Human Bodies: Donation for medicine and research (2011)
http://nuffieldbioethics.org/wp-content/uploads/2014/07/Donation_full_report.pdf
2. EU Directive on the Legal Protection of Biotechnological Inventions
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:213:0013:0021:EN:PDF>

3. Consent

Consent (or authorisation) for the use of human biological material in research, where appropriate, is an integral part of UK tissue legislation^{1,2}; it is one way to deliver transparency and foster trust between researchers and participants; and so should be sought in most situations. Whenever seeking consent, the information provided to potential donors should be proportionate and understandable, supporting the participant to make the decision to donate or not.

Appropriate consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research and should be given appropriate information to be able to make this choice. As an additional safeguard, it should be complemented by independent ethical review of the consent process and proposed protocol³. The General Medical Council guidelines 'consent to research' provides general advice on seeking consent for research⁴.

Participants asked to consent to donation should be properly informed, have capacity to make the decision to participate under no coercion or pressure, and understand the right to withdraw from the research at any time without giving a reason, and in the case of patients, without their future medical care being affected. Information should include the process involved in obtaining samples, any significant associated risks, and if known, what the samples will be used for and how the results of the research might impact on their interests. Donors should be informed of intentions for future storage and use of samples, including the possible sharing of samples with others.

Consent should be given by an appropriate person. Usually this would be the donor themselves, or if they are not able to do so the appropriate proxies should be consulted. Obtaining consent from children and adults not able to consent for themselves is covered in sub-sections F and G later in this section and more information is available in relevant MRC guidance^{5,6}.

There are times when it is not practicable to obtain consent and it is considered ethical to use samples for research without consent, this is reflected in UK legislation and guidance material^{1,2,7,8}. The MRC acknowledges the importance of many existing collections of human biological samples (including pathology archives) in supporting research, even when consent is not in place or is not practicable, desirable or ethical to obtain retrospectively. In this case, research without consent can be undertaken provided the legal requirements are followed, the proposed use of samples (without consent) can be justified, and use would be considered ethical and reasonable.

The MRC proposes two approaches to 'reasonableness':

1. The stronger test – would a reasonable person have refused to allow their samples to be used, if you had asked them?
2. Would a reasonable person be distressed if they discovered that their samples had been used without their consent?

Researchers should consider both justification and reasonableness in proposals when intending to use human biological material without consent, and ensure that the confidentiality of all donors and their associated health and research information is maintained. An NHS Research Ethics Committee will decide whether research use without consent is appropriate.

A. Information sheets and consent forms

One way in which to facilitate the consent process and help the participant make an appropriately informed decision is by providing an information sheet. This should be presented in a form that can be easily understood³. The Health Research Authority (HRA) and MRC have jointly produced guidance on preparing participant information sheets and consent forms⁹. Researchers should be aware that members of some ethnic or religious groups might find some types of research, or donation of certain types of human material, unacceptable, which will influence the sensitivity of approach.

Consent should be recorded in writing when possible (and always when legally required). If the person giving consent is unable to write or is giving verbal consent, this should be clearly documented, including when consent was given and for what purposes. Consent should ideally be witnessed, normally by the researcher, signed by the witness and kept for future reference.

B. Broad and enduring consent

When obtaining consent for use of samples in research, it is important to consider the potential value of those samples for future research.

The MRC, in line with the Human Tissue Authority (HTA), Health Research Authority (HRA), and other UK research funders¹⁰ recommend that broad and enduring consent (also known as generic consent) – that is consent which is broad in both scope and time – should be sought whenever possible. This allows for efficient use of samples, fosters trust with donors and avoids the need to either obtain further consent at a later date or to use samples without consent.

When seeking such broad and enduring consent, participants should be informed that samples may be used in future research, the nature of which may be unknown. A disease area may be specified or for medical research more generally. If relevant, it should be made clear that possible future uses of the samples could include areas of research, which may be viewed as 'sensitive', e.g. where it may reveal clinically relevant findings, or there is the potential to identify participants. Participants should be notified that any future research will conform to all relevant legal, governance and ethical requirements. This is an 'all or nothing' approach to consent, whereby participants agree that they understand the unknown aspects of future use, trust the governance procedures, and express a desire for their samples to be used for the maximal benefit of the research endeavour. If the participant has concerns about any aspect of future use, which cannot be addressed, then broad and enduring consent should not be used.

One way of managing broad and enduring consent is to adopt a **two-part consent** process. The participant is first asked to consent for the planned research, and then to consent for storage and future use of samples in other research, as above. They should also be given the option of consenting only for the first part i.e. the planned project and not the second part, in which case provisions should be made to destroy the samples when no longer required for that purpose. When offering two-part consent, there must be adequate management systems in place to ensure that the donor's wishes can be met with respect to both the specific and broad and enduring elements.

Another possibility is to offer **tiered** consent, whereby the participant is able to consent to some, but not all, future uses of their sample e.g. some categories of research could be excluded¹¹. However, this approach is challenging to manage and requires robust systems that need to be maintained for as long as the sample is held in order to avoid the risk that the donor's wishes are not respected, no matter which consent preferences they select.

More information on consent, including specific guidance on consent for DNA analysis, is available in further legislative documents and guidance^{1,2,7,8,12}.

C. Samples removed from the deceased

There are some ethical and legal considerations specific to the use of human biological material from the deceased*, consent/authorisation being a fundamental principle^{1,2,7-9,12}.

It is important that researchers respect any individual, religious or cultural beliefs which may be pertinent when dealing with donations from a deceased person. As the beliefs of the donor may not be known to the researcher, due sensitivity should always be shown when approaching relatives to ask for consent. Since consent is being sought at a particularly stressful time, relatives should wherever possible, be given time to reflect before making their decision, and it is particularly important that written information is provided for later reference.

In some cases, the balance between the wishes of a deceased donor and those of the relatives may be difficult to reach i.e. the relatives object to the donation despite consent from the deceased before death.

In situations where it is known that a potential donor's illness is terminal, a relationship can be established between the donor, their relatives and the research team before they die. This aids the communication of the wishes of the donor to their family and the researchers. The research team may wish to seek permission from the next of kin to be contacted after the death of the potential donor to inform them about donation and research.

In terms of confidentiality, identifiable patient information about a deceased person should continue to be treated as confidential^{13,14}.

D. Import/export

When obtaining samples of human biological material from abroad, researchers must be satisfied they have been obtained in an ethical manner, in accordance with legislation and ethical standards. It is also important to respect the legislation and appropriate socio-cultural expectations of the country of origin. The Nuffield Council on Bioethics publication 'The ethics of research related to healthcare in developing countries' (2002)¹⁵ and the follow-up discussion paper (2005)¹⁶ highlight the ethical issues involved in importing human biological material from other countries for research.

It is considered good practice to inform the participant during the consent process that their sample may be transported abroad for research, if this is known.

If involved with importing or exporting samples, researchers should be aware of UK legislation and guidance relating to the import and export of human biological material, bearing in mind the law may differ in some parts of the UK^{1,2,17-20}.

In terms of governance, quality and safety, researchers should develop systems to ensure safe and appropriate transit of the sample e.g. sample tracking systems and risk management²⁰. Appropriate regulations and guidance for transport should also be followed^{21,22}.

MRC supported research in other countries involving human biological samples should also be consistent with the UK framework and must comply with this guidance.

E. Gametes, fetal material and embryos

The legal requirements for the use of gametes and embryos in research differ from other forms of human biological material as they are governed by the Human Fertilisation and Embryology Act 1990, amended in 2008. The Human Tissue legislation applies to some research uses of unfertilised gametes and to fetal material^{1,7,18,23-26}. Researchers should be aware of the requirements and specific sensitivities in use of these materials before undertaking such research.

* Donor is deceased at the time the sample was taken.

Guidance on the use of fetal material in research was originally set out in 1989 in the Review of the Guidance on the Research Use of Fetuses and Fetal Tissue, also known as the Polkinghorne Report²⁵. This specified that, where material was obtained from therapeutic abortions, there must be clear separation between the decision to induce abortion and any decision concerning use. Also, the decision to terminate a pregnancy was not to be influenced by consideration of the possible use to which the material may be put. These principles remain valid.

However, the MRC supports the superseding of one recommendation from the Polkinghorne Report by guidance provided in the Human Tissue Authority (HTA) Code of Practice on Consent⁷ whereby the same information should be provided to potential donors in this area as in others.

There are also legal and regulatory implications for the procurement, testing, processing, storage, distribution, import and export of umbilical cord blood cells and cord tissue^{18,27}.

F. Children

The MRC Ethics Guide: Medical research involving children⁶ explores the ethical considerations of research involving children and sets out general principles to ensure research is conducted in an ethical manner. Researchers should be aware of the legal requirements for research involving human biological samples and children in the UK^{1,2,28}. Further guidance is also available^{6,7,9,12,29}.

G. Adults who cannot consent for themselves

The MRC Ethics Guide: Medical research involving adults who cannot consent⁵ outlines the ethical issues pertaining to this vulnerable group, and sets out principles for assessing capacity to consent and for the participation of those who are lacking in capacity to consent to research. There are legal requirements to consider when involving adults who lack capacity to consent in research, which differ according to geographical location in the UK^{1,28,30,31}. There are also sources of further guidance in this area^{4,32-33}.

H. Human biological material collected from colleagues

The same legal and ethical standards apply to obtaining samples of human biological material from colleagues as would to any other participant in research. Valid and freely given consent must be obtained from colleagues. This includes giving information on what samples will be used for, the risks of discovery of health related findings and how these would be handled, how their privacy will be protected and their right to withdraw. Particular attention must be given to the following when asking colleagues to donate samples:

- The possibility of a perceived obligation to participate and the anxiety that colleagues may feel of not wanting to appear obstructive or difficult,
- Ensuring privacy of research results, and
- Uncovering health related findings in situations where donors are likely to be known by those working on their samples.

All requests for donations and consent procedures must be conducted by those who do not have a direct managerial or supervisory role with those being asked to donate. Potential participants should be given the opportunity to ask questions about the research from a person independent of their immediate colleagues if possible.

Independent ethical oversight of research involving colleagues is required. This should be in the form of a positive opinion from an NHS or University REC.

The MRC guidance document 'Working with biological agents'³⁴ and MRC Regulatory Support Centre guidance 'Guidance for staff asked to volunteer blood and/or other samples for research'³⁵ provide further information.

References and related links

1. Human Tissue Act 2004 <http://www.legislation.gov.uk/ukpga/2004/30/contents>
2. Human Tissue (Scotland) Act 2006 <http://www.legislation.gov.uk/asp/2006/4/contents>
3. International ethical guidelines for health-related research involving humans, Council for International Organizations of Medical Sciences (CIOMS) and World Health Organisation (WHO), 2016
<https://cioms.ch/shop/product/international-ethical-guidelines-for-health-related-research-involving-humans/>
4. General Medical Council (GMC) 'Consent to research' (updated 2013)
<https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent-to-research>
5. MRC Ethics Guide: Medical research involving adults who cannot consent (2007)
<https://mrc.ukri.org/documents/pdf/medical-research-involving-adults-who-cannot-consent/>
6. MRC Ethic Series: Medical Research Involving Children (2007)
<https://mrc.ukri.org/documents/pdf/medical-research-involving-children/>
7. Human Tissue Authority (HTA) Codes of Practice: Code A: Guiding principles and the fundamental principle of consent <https://www.hta.gov.uk/hta-codes-practice-and-standards-0>
8. Scottish Executive Health Department HDL (2006) 46. Human Tissue (Scotland) Act 2006: A Guide to Implications for NHS Scotland http://www.sehd.scot.nhs.uk/mels/HDL2006_46.pdf
9. Health Research Authority/MRC: Consent and Participant Information Sheet Preparation Guidance <http://www.hra-decisiontools.org.uk/consent/index.html>
10. UK Research Funders Vision for Human Tissue Resources (2010/11)
<https://www.ukrcr.org/wp-content/uploads/2014/03/Vision+for+human+tissue+resources.pdf>
11. Nuffield Council on Bioethics: Human Bodies: Donation for medicine and research (2011)
http://nuffieldbioethics.org/wp-content/uploads/2014/07/Donation_full_report.pdf
12. MRC Regulatory Support Centre: Human Tissue Legislation Summaries: Consent; Scotland; DNA analysis
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13. DH Confidentiality: NHS Code of Practice (2003)
<https://www.gov.uk/government/publications/confidentiality-nhs-code-of-practice>
14. GMC Guidance on Confidentiality (2009)
<https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/confidentiality>
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4. Ethical Approval

The safety, rights, dignity and well-being of participants and researchers should always be safeguarded. A route to support transparency is to ensure that research involving human biological material undergoes an independent ethical review. There are certain low risk situations where REC review may not be legally or ethically necessary. For example when samples are being used within the terms of consent and there are underpinning governance structures that ensure this, and the research team are not able to identify donors. All direct approaches to donors and consent procedures should be reviewed by a REC. Please see the flowcharts in Annexes 2 and 3 for advice on making decisions relating to ethical approval.

A. NHS Research Ethics Committees

NHS Research Ethics Committees¹ review research that relates to NHS or social care services (Health and Social Care in Northern Ireland) or is required by an NHS REC for legal or policy reasons². A single opinion from one of these RECs is usually valid across the UK. There are also provisions to obtain generic NHS ethical approval for a tissue resource or bank (known as Research Tissue Bank or RTB approval), and potentially for that approval to cover research accessing samples within those banks (subject to conditions)³⁻⁴. If a study does not come under the remit of NHS RECs, researchers can apply for NHS REC review to be provided on a voluntary basis.

B. University Research Ethics Committees

For research that is conducted by University staff outside the NHS (for example where samples are obtained from healthy volunteers and there is no legal requirement for NHS REC review), a University REC will review the proposal. Similarly, where a research study does not legally require ethical review by an NHS REC as above, review may be undertaken by University RECs or those established by other institutions. The Economic and Social Research Council (ESRC) Framework for Research Ethics sets out principles, requirements and standards for such RECs⁵.

References and related links

1. Health Research Authority (HRA) website: Research Ethics Committees.
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4. HRA Research Ethics Committees Standard Operating Procedures
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5. Economic and Social Research Council (ESRC) Framework for Research Ethics (2015)
<https://esrc.ukri.org/files/funding/guidance-for-applicants/esrc-framework-for-research-ethics-2015/>

5. Maximising use and the quality management of samples

Existing collections of samples are often of very significant value for research purposes. With increasing numbers of samples being collected, stored and available for research, and the use of tissue resources or 'biobanks', there is an emphasis on optimising use and ensuring the quality of these samples. In addition, the use of public monies for the collection of samples and research means there is a duty to ensure that samples are used optimally for the benefit of society; and that duplication of effort is minimised¹. It is important that the quality of such samples is known in order for their use to be optimised. The flowchart in Annex 3 provides information on making decisions related to use of existing collections of samples.

A. Quality systems

The MRC requires the adoption of appropriate quality systems in the collection, processing and storage of human biological material. These should be proportionate to the risks involved. These systems use a combination of procedures and records to ensure that researchers know how the samples have been handled and how this will have affected the sample's quality. One of the biggest risks related to research is maintenance of quality. Poor quality can lead to the waste of valuable samples e.g. storage at an incorrect temperature or the use of misidentified cell lines can lead to inaccurate research results or the inability to reproduce research results, all of which are a betrayal of donors' trust.

Quality systems using defined standards will allow researchers to demonstrate that samples are 'fit for purpose' for their own uses and, where applicable, provide assurance that the samples are fit for the purposes of other potential studies or collaborations.

The requirements of a standard will be balanced against the likely uses of the samples. As an example, samples for human application and treatment (not covered by this guidance) will need to meet higher standards than samples for use in research. This is reflected in the available standards and licensing requirements^{2-5, 18}. Standards for the collection, processing and storage of samples for research should be proportionate, practical, realistic and achievable.

A 'quality system' or 'quality management system' sets out the standards being worked toward and how the organisation operates in order to achieve the standard⁶; this information can be captured in a Quality Manual. Standard Operating Procedures (SOPs) give detailed instructions showing how specific tasks are to be carried out. SOPs should be developed on a risk proportionate basis i.e. focussing on risks which are identified as critical. The aim is to document the tasks at a level that will allow an individual repeating the task to achieve equivalent results.

A quality system might include how the sample is collected and transported, how it is processed and stored, how links with associated health data are maintained and how any risks to quality are managed. Using a quality system ensures optimal quality and use of samples, facilitation of sharing and collaboration, and management of collections in line with donors' expectations and wishes.

Some of the issues covered by a quality system for managing a tissue resource are summarised in Box 1 below.

Box 1: Examples of issues covered by a Quality System:

- Management structure
- Governance
- Records and document control
- Access policy and agreements
- Risk assessment
- Health and Safety
- Audit and review
- Staff roles and training
- Premises, facilities and equipment
- Collection, transport, processing and storage of samples
- Quality control and proficiency testing
- Data protection and security
- What happens when things go wrong:
 - Complaints
 - Anomalies, non-conformities and adverse events
 - Corrective and preventive actions

Tissue resources or biobanks provide a number of benefits to researchers, including access to large numbers of samples and disease/patient groups, facilitation of collaborative research and use of samples which may otherwise be forgotten or discarded. However, the standards for quality and types of data collected in different tissue resources may vary. The National Cancer Research Institute's (NCRI) Confederation of Cancer Biobanks (CCB) developed two standards for biobanks to harmonise and assure the quality of the samples and data: these are designed to be generic and this approach is recommended for MRC funded tissue resources^{7,8}.

It is important to have some form of independent input into the management of a tissue resource to achieve transparency. This may be in the form of a steering committee for example, consisting of personnel with appropriate skills and qualifications, as well as lay or participant representation. The responsibilities of the management committees should be clearly defined and their place within the organisational structure of the tissue resource must be clear, ensuring appropriate accountability and governance.

B. Sharing and access

The effective sharing of human biological material and associated data is essential to ensure optimal use and avoid unnecessary duplication of research effort and waste of resources. This should be done with transparency for the donor.

The MRC recommends the use of appropriate material or data transfer agreements to ensure that custodianship of samples is clearly and formally passed onto the new recipients of the samples and set out the conditions under which a recipient is granted access to data or samples. The MRC Regulatory Support Centre produced a list of standards indicating best practice and legal implications for the transfer of samples between organisations⁹. There are legal requirements to be aware of when transferring samples and data internationally¹⁰⁻¹³.

The MRC and partners are building on previous work by the NCRI¹⁴ and STRATUM (Stratified Tissue Repository Alliances Through Unified Methods)¹⁵, identifying and developing resources, such as templates for access policy development and material/data transfer agreements, for widespread use. The MRC Brain Banks network has published such approved resources¹⁶. Additionally, the UKCRC Joint Funders are establishing a Tissue Directory and Coordination Centre to provide a central finder for UK tissue banks, and to provide coordination and guidance to increase harmonisation of standards across the entire biosample lifecycle¹⁷.

The use of Research Tissue Bank ethical approval (RTB approval) can facilitate access to samples, please see Section 4 for more information on ethical approval.

C. Decisions about sustainability and retention of established collections

Established collections of human biological material can provide a valuable source of samples for research, if they are of known quality and hold links to appropriate data. However, long-term maintenance of sample collections requires resources and it is important that the custodian assesses periodically whether old samples are still 'fit for purpose', taking into account both their scientific value and ethical issues. If samples are no longer of value, they should be disposed of safely, respectfully and sensitively, and in accordance with any legal requirements.

Some old and valuable collections of human biological material, established prior to the enforcement of UK human tissue legislation may not have broad and enduring research consent in place. However, the legislation has made provisions for this; ensuring there are routes to prevent useful samples from being wasted^{10,11}.

D. Licensing and Accreditation

Researchers should be aware there may be a legal requirement to obtain a licence from a regulatory body for storage of human biological material^{10,18-20}. Further guidance is available on licensing²⁰⁻²⁵. The Human Tissue Authority (HTA) produced a guide for licensed establishments to measure compliance with the Human Tissue Act (2004) against a set of standards, including standards relating to governance and quality systems²⁶. To ensure tissue resources within NHS Scotland are managed appropriately and similar standards are followed throughout the UK, Scotland has developed an accreditation scheme for the collection and storage of human biological material in NHS Scotland within the Health Science Scotland bioresources²⁷.

References and related links

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8. National Cancer Research Institute (NCRI) / Confederation of Cancer Biobanks: Biobank Data Standard, Collecting, storing and sharing data describing human biological material for research, Version 1 (2014)
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<https://www.hta.gov.uk/policies/licensing-under-human-tissue-act>
21. MRC Regulatory Support Centre: Human Tissue Legislation Summaries: Licensing
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<https://www.hta.gov.uk/hta-codes-practice-and-standards-0>
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<https://www.hta.gov.uk/policies/licensing-under-quality-and-safety-regulations>
24. Human Fertilisation and Embryology Authority (HFEA) website: Applying for a research licence
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27. Scottish Health Department Letter SGHD/CMO(2011)7: Accreditation scheme for the collection and storage of NHS tissue in Scotland
<https://www.sehd.scot.nhs.uk/cmo/CMO%282011%2907.pdf>

6. Use of diagnostic samples/ pathology archives surplus to clinical requirements

Samples of human biological material removed during treatment e.g. surgical procedures, or leftover after diagnostic testing, and those stored in pathology archives can be of considerable value for research, and other purposes e.g. teaching. The value of these samples is further increased if they can be linked to information on the donor i.e. age, medical conditions, treatment and outcomes.

The primary purpose of diagnosis or treatment must always take precedence over any secondary purposes. Many patients expect their samples to be used for maximum effect to benefit others; adopting the position that it is better the material should serve some useful purpose other than simply being disposed of¹.

If researchers require access to diagnostic archives without consent in place for research, this should be conducted within the legal framework provided for this purpose²⁻⁵, respecting the confidentiality of the donor and mitigating the risks of not being able to obtain consent. The flowchart in Annex 3 provides information on making decisions related to the use of existing collections of samples including diagnostic/pathology archives.

Engaging the public on the use of surplus material for research is important to improve transparency and trust between donors and researchers. It is good practice to ensure that patients are informed that their samples may be used for research once all clinical requirements have been fulfilled, for example in a surgical consent form or by a clearly displayed notice to that effect.

One approach is to routinely ask patients undergoing procedures whether they would consent for research use of any excess material. It should be clear to patients that refusal to allow surplus material to be used for research will not affect their treatment in any way. It is acknowledged that many routinely collected diagnostic/pathology samples held to date will not have consent for research in place, and that the law permits research use without consent in certain circumstances⁶.

References and related links

1. NCRI Report: Fostering the Role of Pathology in Research (2009)
<http://www.ncri.org.uk/wp-content/uploads/2013/08/2009-NCRI-Fostering-the-role-of-pathology-in-research.pdf>
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<https://www.hta.gov.uk/hta-codes-practice-and-standards-0>
4. Human Tissue (Scotland) Act 2006 <http://www.legislation.gov.uk/asp/2006/4/contents>
5. HTA information for research tissue banks See Diagnostic archives in:
<https://www.hta.gov.uk/policies/information-research-tissue-banks>
6. MRC Regulatory Support Centre: Human Tissue Legislation Summaries: Consent
<https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/human-tissue/>

7. Financial Issues

A. Financial gain and incentives

The Council of Europe Convention on Human Rights and Biomedicine¹ states that 'The human body and its parts shall not, as such, give rise to financial gain' and the MRC fully supports this principle: the sale for profit (in cash or in kind) of human biological material collected with MRC funding is not acceptable.

Full recovery of costs, based on a transparent accounting system is, however, acceptable. Human biological material does not inherently have any Intellectual Property (IP). However IP can arise from the research utilising the samples and this may be sold or licensed in the usual way.

Payments to those participating in MRC funded research are allowable, provided that the payment is for expenses and time, and is not at a level that would constitute an undue inducement for people to take part in studies.

The ethical issues of financial gain and incentives in research are discussed in the Nuffield Council on Bioethics guidance 'Human Bodies: donation for medicine and research²'.

B. Commercial research/working with industry

The MRC is committed to developing and sustaining close, productive and transparent partnerships with industry in the UK and beyond. Alignment with industry is important in supporting research which will ultimately benefit human health.

It is important that there is clarity of arrangements for allowing commercial access to human biological material originally donated for research projects funded by the public or charity sectors. Where possible, participants should know when their sample or products derived from it may be used by the commercial sector, and the potential benefits of this access. It is also important to let the participant know they will not be entitled to a share of any profits that might ensue, as is also the case for IP rights generated from sample use in the academic sector.

It is not appropriate for any one company to be given exclusive rights of access to a collection of samples made with the benefit of public funds.

The MRC requires arrangements for projects conducted with commercial partners, to be agreed before a project starts and recommends research activities are carried out within an appropriate contractual framework where possible^{3,4}.

References and related links

1. Council of Europe Convention on Human Rights and Biomedicine (1997) Article 21 – Prohibition of financial gain
<https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164>
2. Nuffield Council on Bioethics: Human Bodies: donation for medicine and research (2011)
http://nuffieldbioethics.org/wp-content/uploads/2014/07/Donation_full_report.pdf
3. Intellectual Property Office: The Lambert Agreement/Tool Kit
<https://www.gov.uk/guidance/university-and-business-collaboration-agreements-lambert-toolkit>
4. Commercial Model Clinical Trial Agreements
<https://www.myresearchproject.org.uk/help/hlptemplatesfor.aspx#Contracts-Agreements>

Annex 1: Specific expectations for MRC Institutes and Units

The MRC expects researchers to adhere to the highest ethical standards in medical research and to conform to requirements and guidance set out in this document and by national and international regulatory bodies, professional bodies, and local research ethics and governance frameworks.

In addition, with respect to human biological samples, MRC expects its research Units and Institutes to do the following:

Nominate responsible staff – These individuals should have explicit, well-resourced roles to ensure that these and other research governance expectations are met, and to take part in opportunities to share best practice.

Audits – Audits of samples held should be undertaken annually. Samples should only be stored that have value for research; an audit of collections will identify samples that can be discarded i.e. those that are no longer fit for purpose. This ensures the samples stored are of value for future research and that resources are used efficiently.

Sample records – Units must know which samples are held under which NHS or University REC approval and the terms of consent. For coded samples, systems should be in place allowing Units to determine how samples can be used to ensure that donors' wishes can be met. This means that all samples stored within the Unit (including those that are transferred from other places) are recorded, and their ethical approval and consent status are traceable.

In any recording system the usage and fate of samples should be noted, i.e. which projects they are used in, whether they are transferred to collaborators, disposed of (justification needed), or used up during the research.

Sample transfer – Samples that are no longer held within the Unit should be traceable and transferred under Material Transfer Agreements (MTAs), and following the MRC Standards for Transfer guidance¹.

Sample quality – Systems should be in place that can demonstrate how the samples have been collected and stored so that their suitability for a variety of research projects can be reliably ascertained.

Consent – For all new collections, Units should seek broad and enduring consent for the storage and future use of samples. If tiered consent has been previously used in exceptional circumstances, robust systems should be in place to manage donors' wishes. Retrospective re-consent of donors for existing collections is not recommended unless donors are being contacted for other reasons. Changes to the consent process will require ethical review.

If Units in England do not hold samples under an HTA Licence (NHS REC approval provides an exemption to the need for an HTA Licence), they should have plans in place to manage collections upon expiry of the ethics approval, considering the following: whether samples will be transferred to a Licensed establishment; whether the Unit will apply for a Licence; or if the samples will be discarded (only appropriate if not of significant value).

Research Governance and MRC assurance processes

MRC Head Office should be informed of all inspections that have taken place annually via the Directors' Annual Statement on Internal Control (DASIC) return, unless there are significant findings, in which case information on the findings and actions to be taken should be passed on immediately.

Research Governance is part of the internal audit cycle, as such, Unit and Institute processes for managing sample storage may be audited.

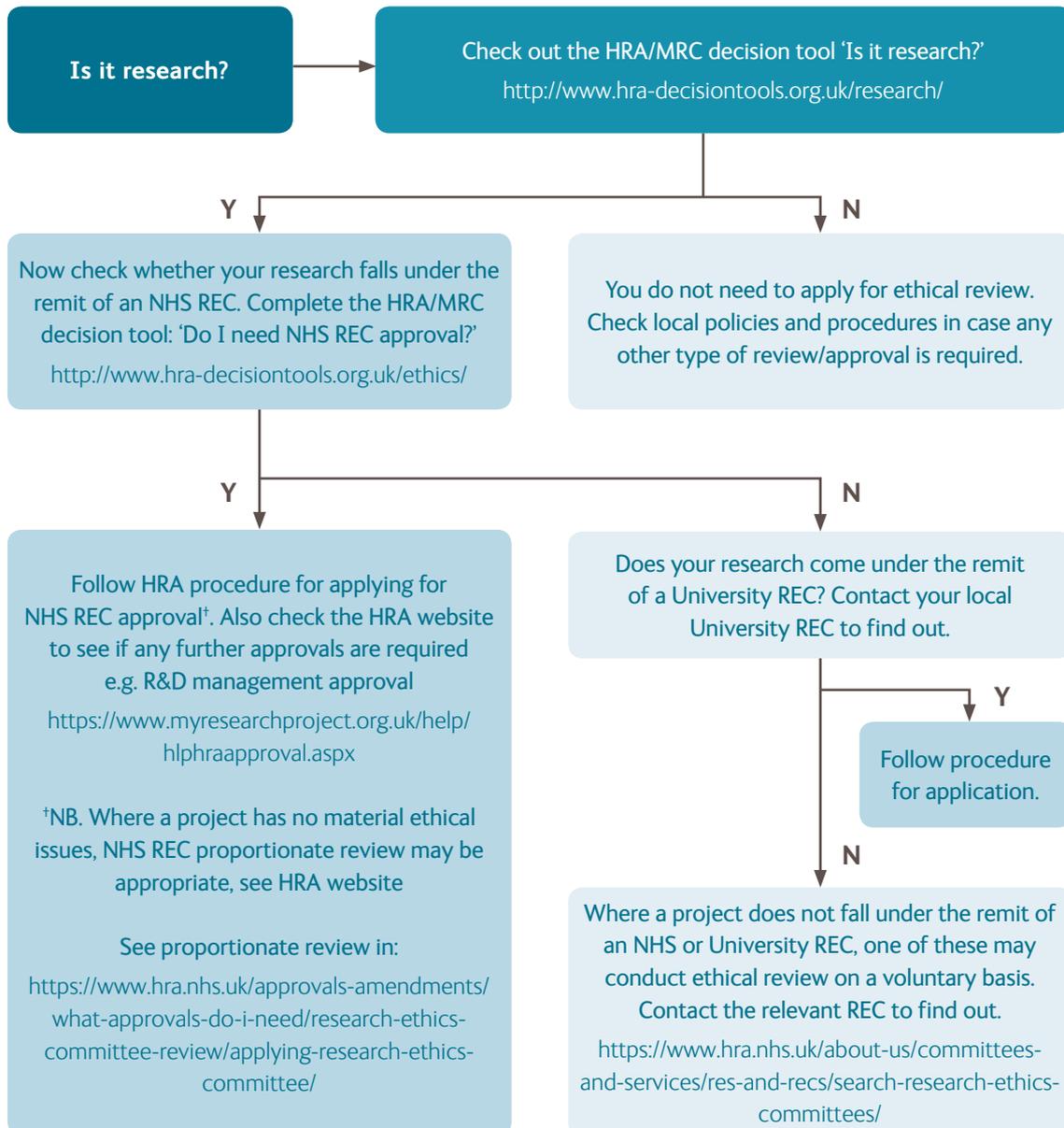
Evidence of maximising research use of sample collections, and plans for future sharing of samples and data will be scrutinised as part of the Quinquennial Review (QQR) process.

The principles outlining the MRC's expectations relating to the conduct of research are provided in the MRC Ethics Series: Good Research Practice guidelines². MRC employees should also refer to the MRC Code of Conduct³.

References and related links

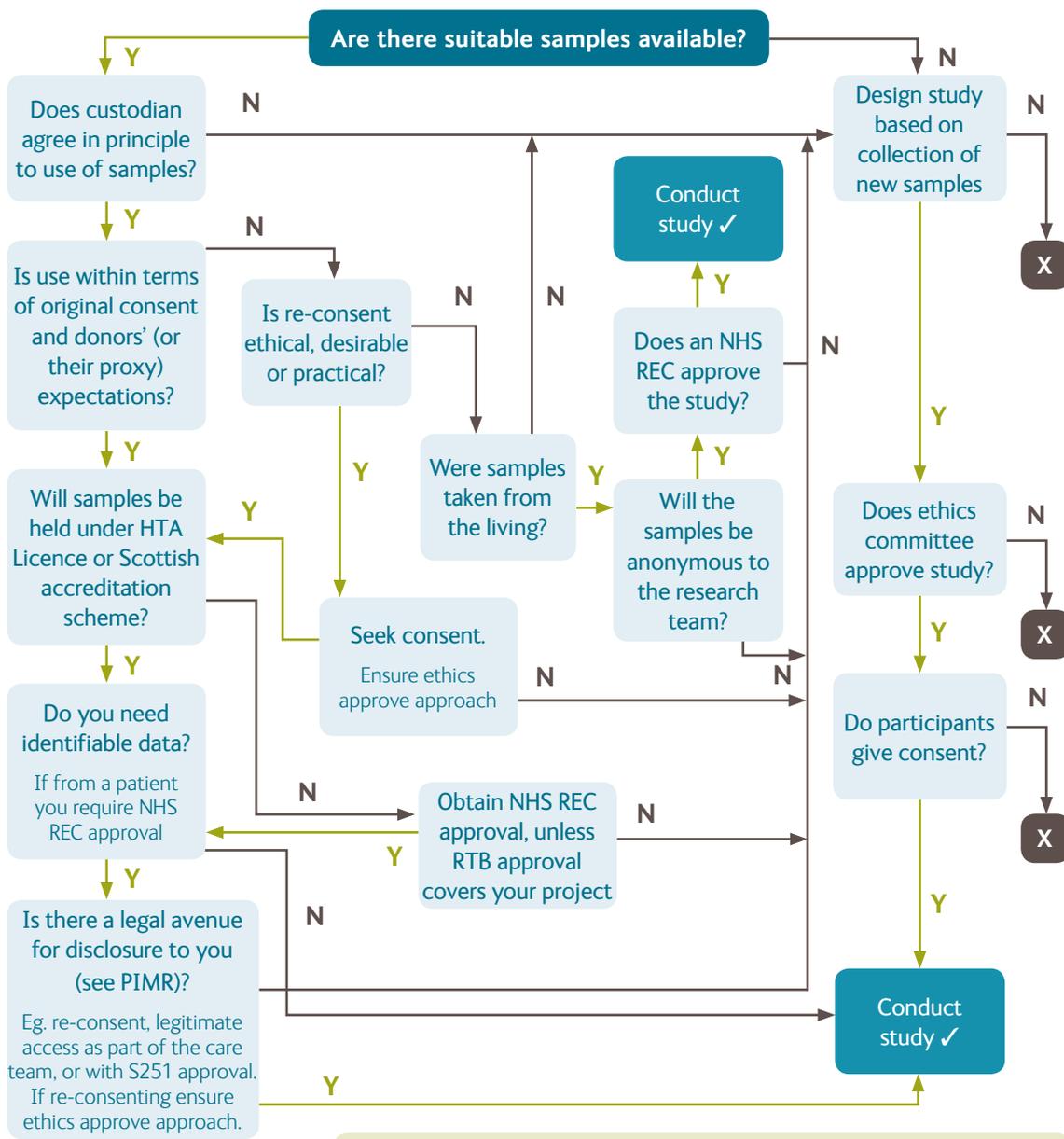
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2. MRC Ethics Series: Good Research Practice: Principles and guidelines (2012)
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Annex 2: Decision tree for applying for ethical approval



Annex 3: Making decisions related to using existing collections of samples, including diagnostic/pathology archives

This flowchart assists researchers when making decisions about the use of existing collections of samples in the UK. Depending on the circumstances there may be additional legal considerations* and/or local procedures to follow.



In Scotland, research involving whole organs released by the Procurator Fiscal requires authorisation (consent) and NHS REC approval.

Key
 X Unable to conduct study Y Yes N No
 RTB approval – Research Tissue Bank ethics approval
 PIMR replaced by MRC Ethics Series: Using information about people in health research
<https://mrc.ukri.org/documents/pdf/using-information-about-people-in-health-research/>

* For more information please see the MRC RSC Human Tissue Legislation Summaries
<https://mrc.ukri.org/research/facilities-and-resources-for-researchers/regulatory-support-centre/human-tissue/>

Glossary and abbreviations

Note 1: The terms human biological material, human biological samples, human material, material and samples are used interchangeably and refer to all biological material of human origin, including organs, tissues, bodily fluids, teeth, hair and nails; but not established cell lines. Many of the principles and approaches in this guidance could equally apply to extracted material such as DNA and RNA.

Note 2: Definitions are taken from MRC sources unless otherwise specified.

Note 3: Terms used throughout the guidance are consistent with legal terminology where relevant, for more details on these terms and definitions, please see the Human Tissue Authority website¹.

Anonymised samples or data have had all identifying information removed, such that it is not possible for the researcher using them to identify the individual to whom they relate. The term is used in these guidelines to refer to both linked and unlinked anonymised data and samples.

- Linked anonymised samples or data are fully anonymous to the people who receive or use them (e.g. the research team) but contain information or codes that would allow others (e.g. the clinical team who collected them or an independent body entrusted with safekeeping of the code) to link them back to identifiable individuals.
- Unlinked anonymised samples or data contain no information that could reasonably be used by anyone to identify the individuals who donated them or to whom they relate.

Broad and Enduring Consent (also known as generic consent): Consent which is broad in both scope and time, usually applicable to a wide range of future medical research use. Future uses of the sample may be unknown, but will be subject to legal and ethical requirements.

Coded samples or data: A code is used in place of identifiers to protect the confidentiality of the individual during routine use, but it is possible for the user to break the code and thus identify the individual from whom they were obtained.

Custodianship: Responsibility for safe keeping of samples and control of their use and eventual disposal in accordance with the terms of the consent given by the donor and any legal and good practice requirements. Custodianship implies some rights to decide how the samples are used and by whom, and also responsibility for safeguarding the interests of the donors.

Ethical approval (positive ethical opinion): Independent ethical scrutiny of the research has been carried out by a Research Ethics Committee (REC) to ensure the safety, rights, dignity and well-being of participants (and researchers) are protected, and a positive opinion of the research has been given by the committee.

Health Related Finding: a finding that has potential health or reproductive importance for a research participant, which is discovered in the course of conducting research, including both pertinent findings and incidental or unsolicited findings.

HRA: The Health Research Authority² was established by the government to promote and protect the interests of patients in health research, and to streamline the regulation of research. It manages NHS Research Ethics Committees in England, the Confidentiality Advisory Group and the Gene Therapy Advisory Committee, amongst others.

HTA: The Human Tissue Authority ensures that human tissue is used safely and ethically, and with proper consent. They regulate organisations that remove, store and use human biological material for research, medical treatment, post-mortem examination, teaching and public display¹.

Human biological samples/material: All biological material of human origin, including organs, tissues, bodily fluids, teeth, hair and nails; but not established cell lines. (Many of the principles and approaches in this guidance could equally apply to extracted material such as DNA and RNA).

Personal information: all identifiable information about individuals, living or dead. This includes written and electronic records and information obtained from samples.

RTB approval: Research Tissue Bank ethical approval.

Tissue resource/establishment/biobank/bank: A tissue bank or a unit of a hospital or another body where activities of receiving, processing, preservation, storage or distribution of human biological samples and cells are undertaken. It may also be responsible for procurement or testing of human biological samples and cells.

Value: Throughout this document samples and collections are described as valuable, this is to reflect the importance of human biological samples to the research endeavour. As such, all collections of human biological samples are valuable, and some may be regarded as of higher value if containing samples that are rarely available.

References and related links

1. Human Tissue Authority (HTA) website: <https://www.hta.gov.uk/>
2. Health Research Authority (HRA) website: <https://www.hra.nhs.uk/>

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