

Transfusion Medicine Research

Contents

1. Introduction
2. Background information
3. Types of research undertaken in Transfusion medicine
4. Areas for future development
5. List of research funders
6. Research posts available
7. Key academic collaborators
8. Medical training in research
9. Scientific training in research
10. The regulatory landscape
11. The National Patient Safety Agency (NPSA)
12. Guide to ethics applications (NRES)
13. Forthcoming courses and meetings

1. Introduction

In the UK Transfusion Medicine research is currently in a good state of health but there is concern that the number of research trainees is declining. Research encompasses a wide range of activities and an active portfolio is essential to the continued provision of a safe and effective blood supply as well as other essential transfusion medicine services. There is a desire to increase the research in the area of hospital transfusion practice and the outcome of transfusion. More systematic research on blood donors is also a priority. Existing active research programmes in blood safety, tissue, cellular and antibody-therapies, immunogenetics and transplantation, protein engineering and recombinant DNA should continue to grow. It is important to increase efforts to fire the imagination of young doctors and scientists, providing them with funded opportunities to train as researchers. This website aims to be a valuable source of research information for current and future doctors and scientists.

The College is supporting research by:

- **Continuing to develop its vital role in training and workforce planning for both clinical and scientific researchers in Transfusion Medicine**
- **Considering, together with other Royal Colleges, the Blood Services and Hospitals, how to establish clinical research networks for hospital transfusion practice and the outcome of transfusion.**
- **Encouraging the development of research into donors of blood, tissues and organs in conjunction with the Blood Services and Public Health Service providers**

- **Continuing to encourage and facilitate research into blood safety, tissue, cellular and antibody-therapies, immunogenetics and transplantation, protein engineering and recombinant DNA.**
- **Arranging meetings and workshops on translational research aimed to inspire current and future researchers.**

2. **Background Information**

Since 2000 there has been a 25% reduction in the numbers of academics and a number of key initiatives have followed:

- a) **UK Clinical Research Collaboration (UKCRC)**. Developed out of the Academy of Medical Sciences report on ‘Strengthening Clinical Research’. Activity is focussed on 5 major areas including building up the research infrastructure (Clinical Research Networks, Experimental Medicine funding, IT), building up the research workforce (new clinical fellows, clinical lecturers and ‘new blood’ senior lecturers), developing incentives, streamlining the regulatory and governance frameworks and the co-ordination of research funding.
- b) **Best Research for Best Health**. Launched January 2006 to direct the government’s strategy for health research with the creation of the National Institute for Health Research (NIHR). Main areas are establishing membership from the academic community (during 2007/2008), development of skills and career pathways, strengthening existing and establishing new funding streams, research centres, governance advice and ethics and Clinical Research Networks.
- c) **The Cooksey Report**. This recommended a ring-fenced ‘Joint Health Research Fund’ for academic clinical fellowships, lectureships and clinical scientists and that future increases in funding should be weighted towards translational and applied research.
- d) **Recommendations for Training the Researchers and Educators of the Future** – report from the Academic Careers Subcommittee of Modernising Medical careers (MMC) and the UKCRC (Walport Report). This recognised a lack of clarity regarding entry requirements for academic medicine, lack of flexibility in the balance between clinical and academic training and a lack of suitable posts.

3. **Types of research undertaken in Transfusion Medicine**

Blood, Stem Cell and Tissue Safety

- Enhancing the evidence base – NBS/MRC Clinical Studies Unit and systematic reviews initiative (collaboration with Cochrane and SNBTS).

- Haemovigilance: data gathering by the Serious Hazards of Transfusion (SHOT) scheme, the National Blood Transfusion Committee and the Steering Committee of the National Comparative Audit of Blood Transfusion. The National Patient Safety Agency (NPSA) is an important partner in this work – see below
- Diagnostic testing for vCJD.
- Malaria – inhibition of erythropoiesis, development of screening tests.
- Genomic screening for hepatitis and HIV; triplex PCR test for HIV, HCV and HBV genomes.
- Review and improve usage of blood products and tissues; role of information technologies.
- Use of granulocyte transfusions in cancer patients, apheresis v buffy coat derived

Cellular and Tissue Therapies

Research is aimed at developing novel cellular and tissue therapies associated with transfusion and transplantation, including:

- Effect of hypoxia on stem cell proliferation and engraftment
- Stem cell development into cardiac muscle and vascular endothelium
- Immunotherapy of cancer and of viral infections e.g. CMV
- Ex-vivo development of erythroid and megakaryocyte cells
- Mesenchymal stem cells in haemopoietic stem cell transplant for prophylaxis or treatment of GVHD .
- Novel tissue grafts –such as decellularised amnion and skin and tendon matrices for tissue engineering

Protein Engineering and Genomics

- The use of recombinant anti-HPA1-a in the treatment of neonatal alloimmune thrombocytopenia
- Antibodies to block platelet activation in heart disease
- Improved detection of anti-platelet antibodies in new immunoassay systems
- Bloodomics Project – genetic markers for the prediction of thrombus formation in coronary heart disease and design of better anti-thrombotic agents
- Recombinant Antibodies to e.g. varicellar zoster-virus
- Mucosal Immunology – Recombinant bi-specific Antibodies
- Blood Group Specific Monoclonal Antibodies

Other research

UK Transplant is involved in research in conjunction with transplant units and both UK Blood Services and hospital-based Histocompatibility and Immunogenetics laboratories. Important themes include

- Impact of HLA matching on outcome of organ transplantation. Data registry studies
- Cell surface markers in lymphocyte differentiation and proliferation
- Cytokine profiles in transplantation
- Tolerance induction – e.g. use of bone marrow, antibodies
- Vascular endothelium – reaction to ischaemia, clonogenic endothelial cells.

Important work in the development of novel blood and tissue products is done in the Component Development Laboratory at Brentwood and Tissue Services Development Laboratory at Liverpool.

Hospital-based research

Much of the research involves relatively small projects and audits in centres with an interest. There is a clear need to gather more evidence for the efficacy of transfusion as done for example in the Canadian Intensive Care (TRICC) Study. Further prospective, randomised, controlled trials of transfusion thresholds and autologous transfusion strategies should be undertaken. Clear endpoints e.g. mortality and health economics are required. Data on blood wastage and financial savings in relation to different transfusion programmes is therefore essential. Important considerations include – avoiding myocardial ischaemia, prevention of primary and re-bleeding in cardiac and other patients (use of thrombo-elastograph and near patient aggregometers), age of red cells, strategies in chronically transfused patients, use of i.v. iron and erythropoietin peri-operatively and in the ITU setting and appropriate blood component use. The key patient groups and transfusion settings therefore include: intensive care units (trauma and burns patients), cardiac surgery, liver transplant, patients with gastro-intestinal haemorrhage and haemato-oncology patients.

4. Areas for Further Development

- Donor-related research (blood, stem cell and tissue donor) e.g. epidemiology and social science aspects; links with projects such as 'Bloodomics' (www.bloodomics.org) Iron balance and the use of iron. This is important in view of the declining donor rate and lack of rigour and application in available market research
- Appropriate and safe use of blood: evidence of efficacy, clinical trials. This is an area where there is both interest and activity but a lack of funds, staff and infrastructure to exploit many of the available opportunities
- Embryonic Stem Cell Research (ESC). There are many opportunities for funding in ESC research and obvious applications in regenerative medicine and drug discovery
- Stem cell therapies – cytotoxic T cells for post-BMT therapy of viral infections e.g. CMV; use of regulatory T cells (TReg); donor leucocyte infusions to manipulate chimerism and treat relapse post-BMT
- Granulocyte transfusions
- Gene therapy - likelihood of increased clinical use
- Cord blood and solid organ transplantation

- Transplantation of non-haemopoietic stem cells e.g. to restore organ function (e.g.liver) and in regenerative medicine

5. **List of funders**

- i. Biotechnology and Biological Sciences Research Council
www.bbsrc.ac.uk
- ii. Medical Research Council
www.mrc.ac.uk
- iii. Wellcome Trust
www.wellcome.ac.uk
- iv. Association of Medical Research Charities
www.amrc.or.uk
- v. British Heart Foundation
www.bhf.org.uk
- vi. National Institutes of Health
www.nih.gov
- vii. Leukaemia Research Fund (LRF)
www.lrf.org.uk
- viii. Cancer Research UK (CRUK)
www.cancerresearchuk.org
- ix. Children with Leukaemia
www.leukaemia.org
- x. Kay Kendall Leukaemia Fund
www.kklf.org.uk

6. **Posts vacant**

New Scientist <http://www.newscientistjobs.com/jobs/default.aspx>

Nature <http://www.nature.com/naturejobs/index.html>

Science <http://sciencecareers.sciencemag.org/>

Universities

Bristol <http://www.bristol.ac.uk/jobs/>
Leeds <http://www.leeds.ac.uk/about/jobs/>
Manchester <http://www.manchester.ac.uk/aboutus/jobs/>
Nottingham <http://jobs.nottingham.ac.uk/>
Liverpool http://www.liv.ac.uk/working/job_vacancies/
Newcastle <http://www.ncl.ac.uk/vacancies/>
Oxford http://www.ox.ac.uk/about_the_university/jobs/index.html
Cambridge <http://www.admin.cam.ac.uk/offices/hr/jobs/>
Imperial <http://www3.imperial.ac.uk/employment>
University College London <http://www.ucl.ac.uk/hr/jobs/>

7. **Key academic collaborators**

8. **Medical Training in research**

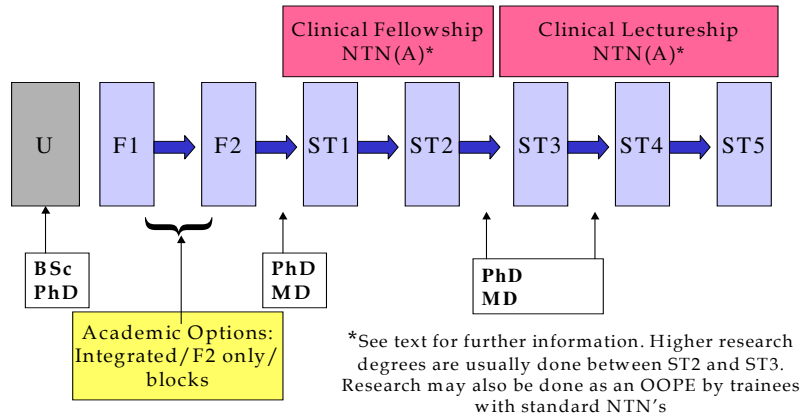
The recommendations of the Report of the Academic Careers Subcommittee of MMC and the UKCRC (March 2005) are summarised below:

Medical schools - intercalated BSc or PhD

Foundation Programmes – these are the integrated F2 programme, academic F2 rotation and 2 year integrated programme.

Specialist Training – dedicated academic training programmes consisting of two phases: (i) academic clinical fellowship leading to a competitive externally-funded training fellowship and either PhD or MD and (ii) clinical lectureship phase leading to CCST. Trainees are given an NTN(A) at entry. Specialist registrars may also be given NTN(A)s and pursue research leading to the award of PhD or MD during their training whilst other trainees with non-academic NTNs may do a PhD or MD as out of programme research (OOPR). It is important to maintain flexibility, allowing trainees to take up research when motivated to do so and also to leave academic programmes if they feel that a research career is no longer appropriate. Trainees in related areas e.g. surgery, nephrology and immunology should also be given the opportunity to undertake research. The availability of adequate numbers of national training numbers (NTN(A)s) is essential. It is important to give trainees adequate support and consideration should be given to the use of mentoring schemes wherever possible. There are many instances where these have been used with great success. Some feel that the MMC agenda has inhibited research since a relative lack of weight is now given to it.

Scheme of Medical Training



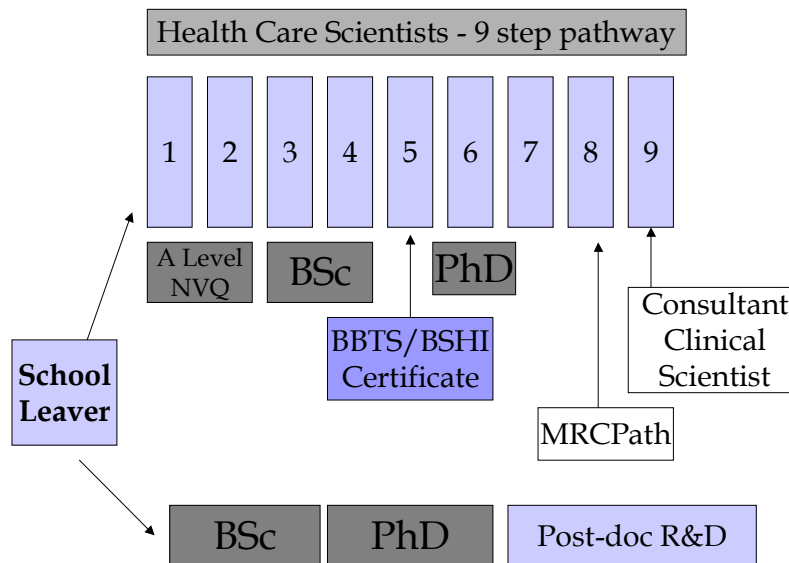
For all trainees subsequent academic progression depends on gaining a further career development fellowship, clinical lectureship or MRC clinician fellowship. Funding for these posts is still inadequate.

A number of fellowships and lectureships have been awarded by major funding bodies including the Department of Health (“Walport” awards), the Higher Education Funding Council for England (HEFCE), the Medical Research Council (MRC) and the Wellcome Trust.

9. Scientific Training in Research

- Modular pathway for clinical scientists with 9 blocks including PhD and MRCPPath leading to consultant clinical scientist position with both service and R&D commitments. MRCPPath taken in Haematology, Immunology or H&I most for Scientists in Transfusion Medicine
- PhD and further research training without service commitment or requirement for MRCPPath
- The Universities of Bristol and Edinburgh offer MSc courses in Transfusion and Transplantation Science
- The British Blood Transfusion Society offers modular training leading to certification for Stem Cell and Tissue Scientists

Scientific Training



10. The Regulatory Landscape

Impact of changes in the regulatory framework for medical research in the UK on basic and translational research

Over the past three years the introduction of two pieces of legislation in the UK has had very significant impact on many areas of medical research. The first and arguably the most significant was the wholesale adoption of the EU **Clinical Trials Directives** (CTD) into UK law as of May 2004. This removed the DDX as a mechanism for trial registration and placed phase I trials on the same basis as phase II and phase III trials with the added burden of the requirement for all trials to follow good clinical practice (GCP). This means that all trials require a sponsor who must accept legal responsibility for GCP compliance. Despite representation from a number of medical research organisations including the MRC and CRUK no provision was made to reduce the regulatory requirements for phase I academic trials. Indeed, upon implementation of the legislation most NHS Trusts were unwilling or unable to accept responsibility as sponsors and some chief executives were advised by their Trust lawyers not to allow haematologists to enrol patients in MRC trials since the role of the sponsor remained unclear. In the case of MRC trials this has been resolved but very significant problems are still faced by academic translational researchers, particularly in the areas of gene therapy or cell therapy trials.

Researchers planning a clinical study first need to determine whether their proposal falls within the definition of a “clinical trial” as defined by the CTD. An algorithm is available in the European Commission guidance document

titled “*Volume 10 Notice to Applicants Questions & Answers*” (Brussels F2/BL D (2006) which should allow one to decide whether the project falls under the CTD. However, according to this algorithm, a laboratory study which does not involve the trial of a medicinal product or device but which requires additional sampling of a patient or is not an epidemiological study is regarded as a clinical trial under the CTD and thus needs a Clinical Trial Authorisation (CTA). This would appear to include all medical research studies on patients except epidemiological data analysis or analyses of discard tissues/blood. In practice it is best to submit your study protocol to the MHRA for a protocol review via the clinicaltrialhelpline@mhra.gsi.gov.uk and marked “Scope – protocol review”.

Trials involving somatic cell therapies fall within the CTD if the cells have been “substantially modified metabolically, pharmacologically or immunologically” during production, in which case they will be regarded as a “somatic cell therapy investigational medicinal product (IMP)”. Plainly this is an imprecise definition and is interpreted differently in different EU member states (MS) and even between individuals within a single regulatory authority. In the UK determining whether one’s cell product has been “substantially modified” requires submission of a request for scientific advice to the MHRA which incurs a fee of at least £2108 or submission of a full application for a Clinical Trial Authorisation (CTA), under the assumption that your product is an IMP, at a cost of £2790.

Having determined that your trial involves an IMP one must submit a CTA application. This is an extremely arduous and complex procedure for most academic units and requires the identification and approval of a sponsor beforehand and must include a product specification file for the cell therapy, an investigators’ brochure and service level agreements with the MHRA licensed IMP production facility, the testing labs involved in monitoring both the product and trial participants and the qualified person releasing the IMP. If approved, the trial must be conducted to GCP and you may be inspected by the MHRA to confirm compliance.

It appears that the CTD was introduced without any assessment of the impact on academic trials or assessment of the increased workload that would fall upon the MHRA which seems to be overwhelmed by it. Numerous publications have detailed the adverse effect of the CTD on academic research; some of which are listed at the end of this article.

Whilst the CTD has delayed translational trials and added very significant expense, the implementation of the **Human Tissue Act** (HTAct) in the UK in April and September 2006 has arguably had an even greater impact on current and future translational and basic medical research. The HTAct was drafted in response to the post mortem retention of organs at Alder Hey and Bristol Children’s Hospital. Not only does this Act cover PM tissues it also includes the storage of tissues and cells for therapeutic use and for research. Although the intention of the legislators is honourable and its application in the cell therapy setting is appropriate and proportionate, its implementation creates considerable difficulties for medical research. The Act allows the storage of

tissues and cells from patients enrolled in ethically approved trials for the duration of research associated with the trial. However, patients cannot give informed consent for research which was not planned at the time of their enrolment and thus tissues or cells stored during the trial cannot be used for subsequent research, even if ethically approved, without transferring the tissues into a HTA licensed research tissue bank. This is an enormously arduous and expensive undertaking and something which is completely outside the experience of most academic researchers. Licensed banks must be operated in the same manner and to the same standards as therapeutic tissue banks with documented training of research staff and complete traceability of tissues entering and exiting the bank. Third party service level agreements are required with researchers using the tissues and these must detail the purpose of the research, its ethical status and how the tissues will be discarded at the end of the study. If the tissues are to be stored after analysis, e.g. tissue sections on slides which have been immunolabelled, then these must be held within a licensed tissue bank or returned to the original bank. How one controls every tissue section taken from a tissue block remains unclear but the aim of the Act is to ensure that the tissue donor can discover what has happened to their tissue at any time and to know where their tissues are held.

HTAct licenses are site specific, not institution-specific, so the direct cost of maintaining research tissue bank licenses is considerable, to which must be added the indirect costs of the paperwork required to manage the bank. We are already aware of groups which will discard research tissues upon completion of trials rather than undertake the process of transfer to a licensed bank. This must be detrimental to future medical research and contrary to the wishes of the vast majority of patients.

The MHRA and the Human Tissue Authority are helpful and sympathetic but are constrained by the legislation which, once again, seems to prove the “Law of unforeseen circumstances” and which have increased substantially the direct and indirect costs of basic and translational research in academic medicine.

References:

Meldolesi, Anna. 2003 EU directive on clinical trials penalizes small sponsors. *Nature Biotechnology*. 21:832.

Hanning, Christopher D and Rentowl, Patricia. 2006 Harmful impact of EU clinical trials directive. Trial of alerting drug in fibromyalgia has had to be abandoned... *BMJ*. 332:666.

Hemminki, Akseli and Kellokumpu-Lehtinen, Pirkko-Liisa. 2006 Harmful impact of EU clinical trials directive – Academic clinical research in cancer seem to have no future in Europe. *BMJ* 332:501-2.

Mitchell, Christopher. 2006 Harmful impact of EU clinical trials directive. ...while paediatric oncology is being scuppered. *BMJ*. 332:666.

Hearn, J and Sullivan, R. 2007 The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK. *European Journal of Cancer*. 43 (1):8-13.

11. **The National Patient Safety Agency**

The National Reporting and Learning System provides a key resource (database) and may be useful in future collaborations between transfusion medicine and NPSA. NHS trusts share patient incidents and other relevant data with NPSA. This is anonymised and confidential and comprises 1.5 million episodes. It conducts commissioned research and is distinct from SHOT although there are some overlaps; it looks at trends. Other NPSA areas include:

- IT specifications and requirements for the transfusion pathway. Some funding here from Connect for Health (pilot project)
www.connectingforhealth.nhs.uk
- Competency training and assessment

NPSA is not a regular funder although transfusion services and hospitals could bid to it for funding. Currently its funds are derived from the Department of Health after approval of a prioritised business plan. There is scope for fast tracking where appropriate. NPSA works with the Patient Safety Research Programme (PSRP) where the need for future research in this area is identified. PSRP provide funding, e.g. for IT developments (lead by Professor Richard Liford, Birmingham). NPSA evaluates and commissions. Attachments or secondments to NPSA might be possible in future. NPSA has no formal academic links. www.npsa.nhs.uk

12. **Obtaining Ethical Approval – NRES**

The following information is from the NRES website:

Facilitating and promoting ethical research

The National Research Ethics Service works with colleagues in the UK to maintain a UK-wide system of ethical review that protects the safety, dignity and well-being of research participants.

Researchers are strongly urged to use IRAS now rather than start any applications in the old on-line form. The feedback on IRAS to date has been extremely positive and already over 10% of research ethics applications have been submitted through IRAS. Data is not able to be transferred from the old ethics online application form to IRAS so researchers are encouraged to take advantage of the increased functionality and benefits of the integration IRAS offers and begin any new applications in IRAS now. IRAS can be accessed at: www.myresearchproject.org.uk

This section is for researchers, research support staff, sponsors and funding organisations.

You can find information on how we are developing the National Research Ethics Service in the Developing NRES section:

<http://www.nres.npsa.nhs.uk/aboutus/developing-nres/>

For the latest information on progress see the news section:

<http://www.nres.npsa.nhs.uk/news-and-publications>

The pilot screening for Early Provision of Advice and Fast Track Review was launched in May 2007. The Operational Plan may also be read:

www.nres.npsa.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=470

- Projects funded by the US Department of Health and Human Services (DHHS)
- Transparency of Decision Making
- NRES Year in Review 2007 / 2008
- Phase 1 trials in healthy volunteers – new arrangements for site-specific assessment
- IRAS updated to include EudraCT data export function

Guidance for applicants or sponsors can be obtained from:

www.nres.npsa.nhs.uk

13. **Forthcoming meetings and courses**

Information can be obtained from the following:

UK Blood Transfusion and Tissue Transplantation Services

www.transfusionguidelines.org.uk

British Blood Transfusion Society <http://www.bbts.org.uk/diary/>

American Association of Blood Banks

http://www.aabb.org/Content/Meetings_and_Events/

British Society for Haematology <http://www.b-s-h.org.uk/Meetings.asp>

British Society of Bone Marrow Transplantation www.bsbmt.org

International Society of Blood Transfusion <http://www.isbt-web.org/>