

**NIHR Evaluation,
Trials and Studies**
ANNUAL REVIEW

09 10



Efficacy and Mechanism Evaluation (EME) programme
NIHR Health Services Research (HSR) programme
NIHR Health Technology Assessment (HTA) programme
NIHR Public Health Research (PHR) programme
NIHR Service Delivery and Organisation (SDO) programme

The past five years have seen concerted efforts to revitalise health research in the UK. Thanks to the NHS, the UK now has an enviable infrastructure for supporting applied and clinical health research, and the ability to improve healthcare based on sound scientific evidence. The vision has been to establish the UK as a world-leading location for health research, delivering health benefits to patients and wealth benefits to the nation. I am delighted to say we are making significant progress towards these objectives.

Our aim has been to transform the practice of research in the NHS, which has called for a huge programme of change. The catalyst has been the National Institute for Health Research (NIHR), which has established a comprehensive research system and enabled high-quality research in the NHS to thrive. Important features of the system are a highly trained workforce, as well as essential infrastructure, facilities and networks that enable large-scale clinical research, all underpinned by the systems needed to expedite research and safeguard patients and the public.

A key piece in the NIHR jigsaw is the research itself. The programmes run by the NIHR Evaluation, Trials and Studies (NETS) Coordinating Centre are at the heart of the NIHR's work, supporting research that is both relevant to users' needs and of the highest possible quality. The case studies in this Annual Review illustrate how NETS projects provide decision-makers with reliable and relevant information about key issues influencing effective and cost-effective healthcare delivery.

The recognised success of the HTA programme was one reason why funding for health research has grown so significantly over recent years. It is very welcome to see the many ways in which this funding is generating the vital evidence on which sound choices in healthcare delivery are being made. The impact factor for the HTA journal series has now risen to 6.9. This is testimony to both the scientific quality and importance of the HTA programme to the NHS.

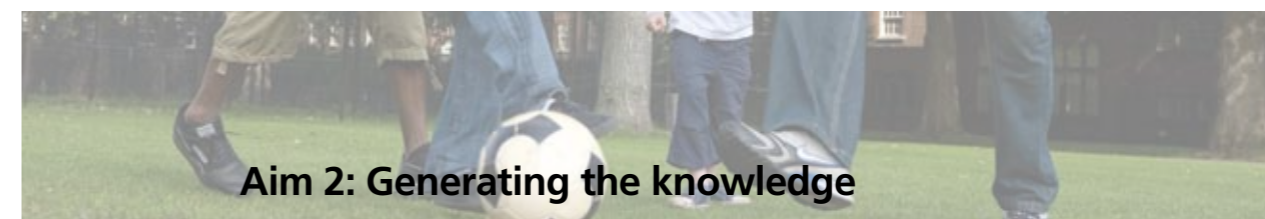


Professor Dame Sally C Davies
 Director General of Research and Development,
 Department of Health

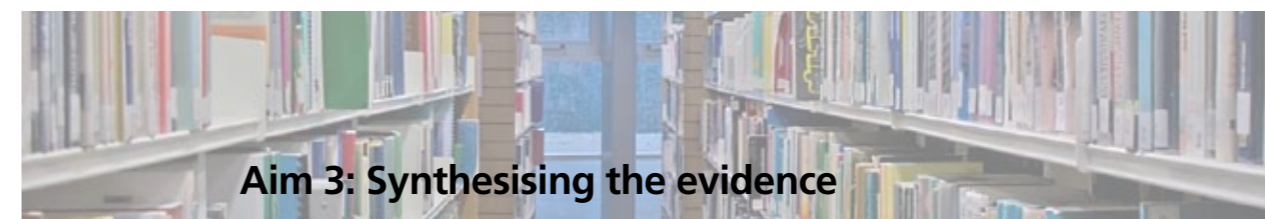
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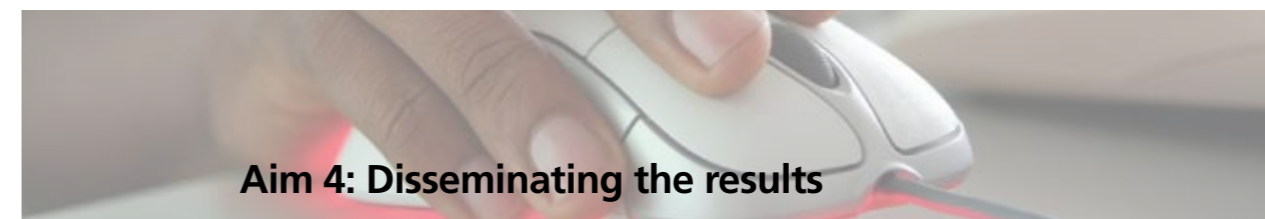
Aim 1: Identifying the need



Aim 2: Generating the knowledge



Aim 3: Synthesising the evidence



Aim 4: Disseminating the results

NHS R&D: A pathway to future health

There are four complementary pillars to developing a successful health service: audit, training, quality assurance and research. Research is therefore not an adjunct to healthcare but an integral part of its effective delivery – identifying what treatments work, how they can be delivered most cost-effectively, and where future therapies are likely to come from.

It may be tempting, especially in difficult financial times, to focus on short-term targets and needs, and to neglect longer-term planning. But it is always best to make difficult decisions on the basis of reliable evidence.

The NHS provides the UK with a unique infrastructure for high-quality health research. The development of the National Institute for Health Research (NIHR) has been aimed at establishing the NHS as a world-leading organisation hosting health research, but always focused on the ultimate aim of enhancing the care provided to patients.

Given the large sums invested in health research in the NHS in recent years, it is reasonable to ask what are the patient benefits. There are tensions in responding to this: 'success' is ultimately and rightly judged according to impact on patients and service delivery. But original research can be slow and it may take many years to show clear patient benefits, as emphasised in a recent report (1). The role of research is also to generate the knowledge on which this impact can be achieved, and to facilitate its use to shape policy and practice. Research rarely generates instant answers or drives instant implementation.

Nevertheless, we as part of NIHR can work to maximise the impact of research. We need to keep close to those who need and will use the research: to understand what their questions are, and how research can provide answers to them. Our research needs to be pragmatic and rooted in the realities of service delivery. Crucially, the research that we support must be of high

quality, generating relevant and reliable results. We need to help our researchers to deliver their research efficiently, and then to disseminate their findings in a way that is helpful and timely for users. We have many examples of this across our programmes, detailed later in this report.

Supplying the evidence for evidence-based medicine lies at the heart of all of the NETS programmes. This Annual Review provides examples of where NETS research is having an impact at different points along the translational pathway, or has the potential to do so in the future.

The NETS programmes

The Efficacy and Mechanism Evaluation (EME) programme, funded by the Medical Research Council, targets one of the key translational gaps. It exploits promising first-in-human studies and translating them into clinical evidence of efficacy, while taking the opportunity to understand more about the disease or how the intervention works. The Health Technology Assessment (HTA) programme is the UK's largest single programme for health research, supporting clinical trials and other research of direct relevance to patient care. In common with other NETS programmes, its research is always led by the needs of the NHS, patients and the public, as identified by researchers or by NHS users or by those who will determine NHS policy: for instance it provides the systematic technology reviews and analyses that underpin guidances from the National Institute for Health and Clinical Excellence (NICE).

The Service Delivery and Organisation (SDO) programme examines how the NHS works and how it can work better, including how to implement research within the day-to-day realities of the health service, while the Public Health Research (PHR) programme targets interventions outside the NHS. The new Health Services Research (HSR) programme tackles a wide variety of research to improve the delivery of care and the patient's experience of the NHS.

Integration

Although they have their own specific objectives, the NETS programmes also operate as an integrated whole, and form part of a broader NIHR portfolio. This integration was apparent in the rapid response to the H1N1 swine flu pandemic. Working closely with the Department of Health, the NIHR swiftly mobilised to identify key information needs and then to commission research (as well as providing funds for researcher-led studies). This also provided an opportunity to build on established relationships with other parts of NIHR such as the research networks, and with regulatory agencies, which we will develop further in the future. This coordinated response, with numerous bodies working together, generated important findings at remarkable speed (2,3).

The NETS programme portfolio has been through considerable change in recent years and its budget has grown substantially.

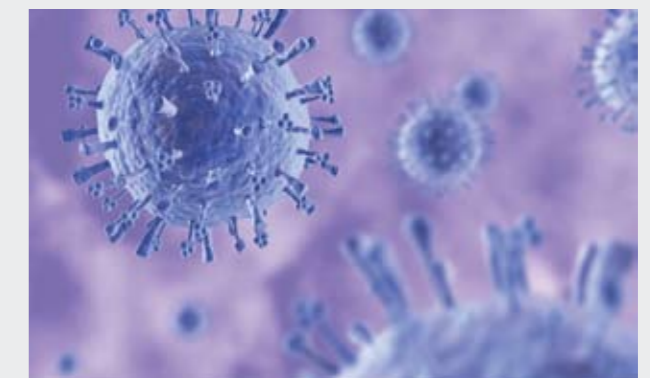
It has been important to ensure that new programmes get off the ground, but also that all the programmes are joined up and maintain strong quality assurance. I am very pleased to report our successes in this and I wish to thank all of those who have worked so hard to ensure this. We are already starting to see the results of this: sometimes in the form of delivered study findings that have a clear impact on patient care. And sometimes in high-quality studies underway that I am confident will ultimately also help to improve the care the NHS provides.

1. Health Economics Research Group, Brunel University, Office of Health Economics, RAND Europe. Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK. *Academy of Medical Sciences, Medical Research Council, Wellcome Trust*, November 2008
2. Walley T, Davidson P. Research funding in a pandemic. *Lancet*. 2010 Jan 20. [Epub ahead of print] PMID: 20096451
3. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet*. 2010 Jan 20. [Epub ahead of print] PMID: 20096450



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and Professor of Clinical Pharmacology, University of Liverpool

H1N1 pandemic influenza virus.





Involving patients and public

NIHR and the NETS programmes

The NETS programmes are run by the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton on behalf of the National Institute for Health Research.

UK Government support for medical research is channelled primarily through the National Institute for Health Research (NIHR) and the Medical Research Council (MRC). Broadly speaking, the NIHR funds later-phase health research, which has the potential to influence the delivery of healthcare to patients, while the MRC supports basic and early clinical research. The two bodies work closely together, overseen by the Office for Strategic Coordination of Health Research (OSCHR) to ensure that there is a continuum of research opportunities along the translational pathway and to ensure activities are coordinated.

Following recommendations made in the Cooksey Review, health research funding has grown, with annual expenditure across the five NETS programmes currently anticipated to amount to £78m in 2010/11. The NIHR funds the HSR, HTA, PHR and SDO programmes, with contributions from the Chief Scientist Office in Scotland (the HSR, HTA and PHR programmes), the National Institute for Social Care and Health Research in Wales (all four programmes), and Health and Social Care Research and Development, Public Health Agency, Northern Ireland (the PHR programme).

While MRC and much charity funding focuses on early stages of the translational pathway, NETS projects typically focus on interventions where at least some evidence of efficacy already exists. In the NHS, the projects provide additional information that can guide whether interventions are suitable for use – are they better than alternatives and do they represent cost-effective use of NHS resources? Such research is unlikely to be supported by commercial agencies, which principally focus on research to establish efficacy. Beyond the NHS, high-quality research evidence can enable policy-makers to identify effective ways to tackle health inequalities and improve public health.

All aspects of healthcare delivery are covered by the NETS programmes – from the ‘what’ (which treatments are effective and cost-effective) to the ‘how’ (how should services be organised to deliver high-quality care to patients). Most research projects are focused on healthcare within the NHS, though there are other domains in which NETS-funded research can have an impact, most notably public health. Evidence-based approaches can suggest ways to promote healthier living and prevent disease, and in other ways promote public health and well-being. Through these routes, NETS research has the potential to make a substantial impact on the quality of healthcare delivered in the UK – and hence benefit the health and wealth of the nation.

Answering the questions

Several bodies are key users of research findings generated through NETS funding. These include advisory bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee, as well as agencies with commissioning responsibilities within the NHS, Foundation Trusts, Primary Care Trusts

and so on. Other important clients include patients, and senior policy-makers addressing health priorities, including the national ‘health tsars’. Research findings are also shared throughout the health and research communities via routes such as NHS Evidence and UK PubMed Central.

The NETS programmes are distinctive in being ‘needs-led’ and ‘science-added’. The starting point for research is a clinical uncertainty or gap in knowledge; research is the route by which the uncertainty can be resolved or the missing information generated. Hence, most funding streams combine both ‘relative priority’ and ‘scientific quality’ assessments in the review of grant applications, and projects are actively monitored to ensure they ultimately provide information that contributes to addressing these knowledge gaps and uncertainties.

Most programmes have both commissioned and researcher-led workstreams. Commissioned workstreams start with the information needs of decision-makers who are typically, but not exclusively, within the NHS. Researcher-led workstreams are open calls enabling researchers to apply for funding for topics they have identified, often within broadly defined themes of importance to the NHS or public health.

Patient and public involvement

The NETS programmes are committed to involving public representatives at all stages of research. NETS panels include lay members, who contribute to strategy development and priority setting and, when appropriate, to assessment of funding applications. With the NHS Constitution emphasising the right of patients to take part in health research, researchers are encouraged to involve patients and the public in research projects.

Aim 1: Identifying the need

The NETS programmes work closely with policy-makers, professionals and the public to identify areas where high-quality evidence for decision-making is needed.

The programmes assimilate input on a wide range of issues and priorities, identifying those of particular significance to the NHS. These may be short-term concerns, such as the threat posed by H1N1 swine flu, or long-term issues, as with the potential health impact of obesity. Close relationships are maintained with the National Institute for Health and Clinical Excellence (NICE), which uses HTA-commissioned technology assessments to inform its guidance, and the National Screening Committee, the Government's advisory body for health screening.

Establishing and responding to priorities

The NETS programmes have developed a range of complementary approaches to establish research priorities to meet health needs. This work builds on the extensive experience in identifying and prioritising research developed by the HTA programme since it was launched in 1993. Sufficient flexibility is maintained to enable the programmes to respond swiftly to emerging priorities.

The rapid response to the H1N1 swine flu pandemic showed how quickly the health research infrastructure and research community could be mobilised in times of national need. The lead was taken by the Department of Health, which sought advice from its Scientific Advisory Group on Emergencies (SAGE). SAGE identified several urgent research priorities, received by the National Institute for Health Research (NIHR) at the beginning of June 2009. Following an assessment of these priorities, the NETS

programmes commissioned nine projects of national importance.

With the trajectory of the pandemic uncertain, speed was of crucial importance. The swift response extended to other parts of NIHR, and to other associated bodies such as the Medicines and Healthcare Products Regulatory Authority, which approved clinical trial applications, and the National Research Ethics Service, which activated an emergency policy so ethical approvals could be secured rapidly. The first results from commissioned research appeared in *The Lancet* in January 2010.

Addressing a longer-term threat to health, a joint call on obesity was launched in 2009 by the HTA and PHR programmes as part of the NIHR Obesity Research Strategy.

Safeguarding scientific quality

Experts are involved at various stages by the NETS programmes, including the public and a wide spread of professional expertise as well as clinicians and academics. Rigorous scientific assessment is based on academic peer review and oversight by panels of experts knowledgeable in particular areas of science and medicine.

In the case of the PHR programme this extends beyond the NHS. As public health falls within the spheres of influence of several professional disciplines, the programme draws upon expertise in a range of areas, including local government, the charitable sector and social care. The scientific quality of projects is addressed through the involvement of leading academics.

Seeing disease more clearly

Better diagnostics can help patients get treatment more rapidly and avoid unnecessary interventions.

Accurate diagnosis is critical – treatments will only ever be effective if they are used on the right patients. It can also ensure that people are not subject to interventions that they do not need. While evaluation of interventions has received much attention, diagnostic tests have tended to receive less scrutiny. The 'Diagnostic tests and test technologies' themed call, launched by the HTA programme in 2009, sought to encourage more evaluation in this area of growing importance. Ultimately, 16 projects were funded – 13 trials and three evidence syntheses.

Patient care has the potential to be radically changed by new diagnostic techniques – particularly non-invasive imaging techniques such as magnetic resonance imaging (MRI), which can provide a detailed internal view of body tissues. Several of the projects will assess the potential use of MRI, for example to characterise prostate cancer,

to identify 'mini-strokes' (transient ischaemic episodes), and as a possible alternative to keyhole surgery in women with chronic pelvic pain.

New approaches to diagnosis based on computed tomography (CT) are also being investigated, and projects will assess its ability to identify bowel cancers at risk of early spread, and early stages of lung cancer.

Other projects are evaluating more traditional biochemical tests, for example in cardiac disease and to identify those at risk of complications from pre-eclampsia during pregnancy. In behavioural conditions, diagnosis may rely on questionnaires or similar tools, and one project is testing a tool to identify risk of self-harm in offenders.

All the projects are building on the potential of existing tools, testing not just their diagnostic abilities but also their usefulness to the NHS or other agencies, practicalities of use and the likely cost-effectiveness of wider implementation.

Computed tomography (CT) scanning is increasingly being used in a diagnostic setting.



Spare the lungs, save the patient

For adults suffering severe respiratory failure, oxygenating blood outside the body is significantly better than lung ventilation.

Once a patient's respiratory system begins to fail, the drop in oxygen supply to the body's tissues is potentially life-threatening. Mechanical ventilation can increase the supply of oxygen, but may inflict further damage on lungs. An alternative is to adapt the gas-exchange equipment used during heart bypass procedures, in which blood is oxygenated outside the body (extracorporeal membrane oxygenation, ECMO). Now, a specially commissioned clinical trial has produced the world's first systematically acquired data on ECMO – suggesting it is significantly superior to mechanical ventilation for adults with severe respiratory failure.

By the late 1980s, ECMO was being used routinely in the USA to keep babies alive. As its use became more widespread, there was growing concern that its effectiveness had never been assessed in a randomised controlled trial. A landmark trial published in 1996 however, demonstrated the life-saving value of ECMO in babies. A similar picture emerged in the 1990s, as ECMO began to be applied again to adults with severe respiratory failure. With some strong opinions favouring the status quo and others advocating ECMO, it was clear that another definitive clinical trial was needed.

The CESAR trial proposed by Giles Peek and colleagues at Leicester University randomly assigned 180 patients aged 18-65 to either

ECMO or to continued specialist treatment. The patients all had severe (but potentially reversible) respiratory problems, such as pneumonia or lung injury. Patients in the ECMO arm were transferred to Leicester for consideration of ECMO treatment.

CESAR again provided very clear evidence of benefit. While 47 per cent of patients treated conventionally survived to six months without disability, this figure rose to 63 per cent in those receiving ECMO. In other words, ECMO leads to one extra survivor for every six patients treated.

ECMO is, however, more expensive than mechanical ventilation. Nevertheless, economic modeling suggested that an additional quality adjusted life year (QALY) would cost around £20 000, a figure generally viewed as representing acceptable value for money. ECMO costs are similar to those of a lung transplant.

ECMO assumed a higher profile in 2009 thanks to its use on patients badly affected by H1N1 swine flu. Two further hospitals, Papworth and the Royal Brompton, were earmarked to provide 'surge' capacity. Now the National Specialised Commissioning Group is in the process of identifying centres that will offer adult ECMO on a more routine basis.

Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374(9698):1351-63



Giles Peek, who has led a large trial testing extra corporeal membrane oxygenation for adults with severe respiratory failure.

A good death

What can be done to improve care during patients' final days?

No matter how good medical care is, ultimately it becomes an unwinnable battle and the inevitable has to be accepted. The main aim then becomes to make a patient's final hours as comfortable as possible. But how should palliative care be delivered? Several projects funded by the SDO programme will provide complementary perspectives on this important but sensitive area.

Cancer care and the hospice movement have done much to raise awareness of palliative care. Patients' wishes are of prime importance, and most would prefer to spend their final hours at home. However, this is easier to manage for cancer patients than other groups, as the course of disease is generally more predictable. Overall, more than half of people end up dying in hospital.

To shed light on this issue, Professor Merryn Gott, Dr Clare Gardiner and Professor Christine Ingleton at Sheffield University will be undertaking a census of all older patients at two hospitals serving contrasting populations, to gain a comprehensive view of patients', families' and healthcare professionals' perceived needs, preferences and attitudes. A complementary systematic review led by Dr Fliss Murtagh at King's

College London will draw together published findings on patients' preferences for place of care/death, where they actually end up dying and what factors influence the final outcome.

One reason why people may end up dying in hospital is a lack of out-of-hours care – an area currently undergoing major revision. To find out how out-of-hours care provision is affecting end-of-life care, a team led by Professor Julia Addington-Hall at Southampton University is examining five organisational case studies to map out all possible patient journeys through the healthcare system during the terminal phases of illness. This should reveal a clearer picture of bottlenecks and the factors associated with better experiences for patients and families.

Finally, Professor John Ellershaw at Liverpool University and colleagues will be formally assessing the Liverpool Care Pathway, widely regarded as the epitome of good practice in palliative care. Initially developed for hospitals, it provides advice and guidelines for all members of healthcare staff who may find themselves caring for someone in the last hours or days of life. Although it is being rolled out widely across the NHS, it has not been evaluated in detail. The new project will evaluate its impact in a range of intensive care units and nursing homes in England.

Several SDO projects are evaluating the delivery of palliative care and patient journeys through the final days of illness.



Seeds of change

Will a Royal Horticultural Society (RHS) initiative to promote gardening in primary schools change young children's eating habits?

Diets rich in fresh fruit and vegetables are well known to be good for health. Growing such produce may also be beneficial, providing fresh air and exercise. So a Royal Horticultural Society initiative to promote gardening in primary schools in four London boroughs might be expected to improve health, encouraging children to eat more fresh fruit and vegetables. But growing is not the same as consuming. With funding from the PHR programme, Professor Janet Cade and colleagues in Leeds are assessing the initiative's impact on children's eating habits.

The project will be run as two randomised trials. Some schools are undertaking the gardening project with intensive support

from the RHS, while others receive less-intensive support, with twilight sessions for teachers each term. These schools will be compared with each other, and with schools in neighbouring boroughs that are not participating in the RHS initiative.

Around 2000 year 3 and year 4 children (aged 7–10) from 58 schools will participate. Their eating habits will be studied using a validated tool for assessing food and nutrient intake, at baseline when the RHS project begins then again two years later, after two growing seasons. Their attitudes to diet will also be assessed.

The trial should reveal whether the RHS scheme has any long-term impact on children's eating habits – and more generally whether exposure to gardening encourages children to adopt healthier eating and lifestyles.

A project funded by the Public Health Research programme is testing whether a schools gardening project affects children's eating habits.



Needs-driven

Professor Dame Sally C Davies is Director-General of Research and Development, Department of Health.

“The NHS provides a tremendous infrastructure for health research. As well as being high quality, this research needs to reflect the NHS's needs – and that's precisely what NETS programmes projects do.”

Quality...

Dr Martin Ashton-Key is a public health consultant and currently medical adviser to the National Specialised Commissioning Team; he was previously a consultant adviser to the HTA programme and is a member of the HTA programme's Pharmaceuticals Panel.

“One of the crucial things about the internal workings from start to finish is that topics reflect the needs of the NHS and patient groups within it. The internal processes that take an idea through prioritisation to developing the question to commissioning and then actually doing the research – and, importantly, overseeing that research function – is very robust, rigorous and transparent. As a commissioner of services, and having seen it work on the inside, I'm completely assured that it's a fair and robust system.”

Benefits...

Val Carlill is a lay member of the Psychological and Community Therapies Panel of the HTA programme:

“People who work within the NHS are very much ‘in the groove’, so they might not question things that a lay perspective would. It's difficult to get the balance between benefits to the NHS and benefits to the patient. Maybe the lay perspective is slightly more patient-oriented, simply because the professionals have got the costs and the finances in their faces all the time, and they know there are limits to what they can do and difficult choices to be made.”

Research topics reflect the needs of the NHS and patient groups.





Supporting public health

Aim 2 Generating the knowledge

Where important gaps in knowledge exist, they can be filled by new research. NETS programmes commission research with specific objectives in mind, alongside themed calls and researcher-led funding streams that provide more scope for researchers to identify potentially important areas of study.

Research projects span several points of the translational pathway. For example, research funded through the EME programme targets an early stage, aiming to drive promising interventions towards practical application.

While clinical or public health relevance is crucial, it is an additional requirement rather than a replacement for the scientific quality control achieved by peer review. Many NETS-funded studies are published in high-impact journals, evidence of their high quality and value to other researchers, as well as to health service decision-makers and professionals outside the NHS. Research is not a quick fix, however. Projects typically take years to plan, carry out, analyse and write up. If the findings are to be reliable, this investment in time is essential.

Research is often undertaken to test whether a new procedure is superior to that already used. Often this turns out to be the case, but sometimes a trial shows no benefits or no significant differences. Even such trials are valuable, however, confirming that existing interventions are the best available and feeding into a larger pool of knowledge that can be analysed by research synthesis.

This year has seen a greater emphasis on integrating programmes and offering a high-quality service to applicants. NETS programme staff often work with applicants to develop bids, and proposals can now be transferred internally if they are a better 'fit' with a different programme. Programme staff also maintain regular liaison with grantholders, offering advice and helping projects stay on track.

Less blood loss, less life lost

An agent that prevents breakdown of blood clots significantly improves survival after traumatic injury.

Injury is the leading cause of death for young adults and children in the UK, and world-wide injury is responsible for more deaths than HIV, tuberculosis and malaria combined. Around half of severely injured patients who make it to hospital die from blood loss – about 600,000 deaths a year. Still more suffer bleeding-related fatal brain injury or organ failure. Halting blood loss is thus crucial, and agents that promote blood clotting might substantially affect survival. Indeed, the international CRASH-2 trial, coordinated from the London School of Hygiene and Tropical Medicine, has found that a cheap and widely available drug, tranexamic acid, significantly improves survival of severely injured patients.

One of the largest studies of traumatic injury ever undertaken, the CRASH-2 trial involved over 20 000 patients, from 274 hospitals in 40 countries. A randomised placebo-controlled trial, CRASH-2 looked at the impact of tranexamic acid, given as soon as possible after injury, on survival at four weeks.

Tranexamic acid reduces clot breakdown, tipping the scales in favour of clotting. Although it is routinely used in surgery to reduce bleeding, little evidence has been available on its possible use in trauma.

The CRASH-2 trial found that patients given tranexamic acid were significantly less likely to die – risk of death due to bleeding was 15 per cent lower, and all-cause mortality around 10 per cent lower.

Although there was a concern that tranexamic acid might result in more heart attacks or strokes, due to blockage of blood vessels by undigested clots, CRASH-2 found no evidence for increased risk of such conditions. If anything, they were actually less common in patients receiving tranexamic acid.

By reducing deaths from bleeding by around a sixth, tranexamic acid could save as many as 100 000 lives a year. The treatment could save lives in all countries, but significantly for low- and middle-income countries, tranexamic acid is cheap and readily available, and hence likely to be highly cost-effective.

CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised placebo-controlled trial. *Lancet* (doi:10.1016/S0140-6736(10)60835-5)

Extensive blood loss can dramatically reduce survival chances after serious injury.



A single shot

A single dose of radiotherapy during surgery can prevent the most common form of breast cancer from recurring.

Invasive ductal carcinoma is the most common form of breast cancer, accounting for around 80 per cent of cases. Early-stage tumours are typically excised surgically, conserving as much breast tissue as possible. To prevent recurrence, women then undergo radiotherapy of the entire breast in daily sessions lasting several weeks. However, an international clinical trial led by Professor Michael Baum at University College London with Dr Jayant Vaidya and Professor Jeffrey Tobias, has shown that localised radiotherapy at the time of surgery is just as good at preventing recurrence.

Conventional treatment is highly effective. However, the radiotherapy sessions are gruelling and a significant imposition on women. They are carried out to prevent other clusters of abnormal cells developing into secondary cancers. However, when they do recur, secondary tumours generally arise from the same area of breast as the initial cancer. This led to the idea that radiotherapy would be just as effective if restricted to the original tumour site.

To test this idea, the TARGIT-A (targeted intraoperative therapy) trial compared conventional surgery and whole-breast radiotherapy with a single procedure combining surgery and localised radiotherapy.

The trial involved more than 2000 women aged 45 and older from nine countries, all with early-stage invasive ductal carcinoma.

Women were followed up regularly, every six months for 5 years, and then annually up to 10 years. The number of recurrences was very low, and almost identical in the two groups.

Although long-term follow-up is continuing, the main danger period for recurrence is around two to three years – and localised radiotherapy is a match for conventional treatment at this key point. The TARGIT-A group experienced more fluid build-up in the wound area, but this was more than offset by fewer side-effects, such as pain – as well as the greatly reduced treatment burden.

Targeted therapy has a further advantage, reducing the demands on radiotherapy services – breast cancer representing up to a third of a typical centre's workload. Preliminary economic modelling suggests that a switch to targeted therapy could save the NHS some £15 million a year. The success of TARGIT-A also raises the question of whether a similar approach would be suitable for breast cancer in other patient groups, such as young women, who usually experience more aggressive forms of the disease.

Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* (doi:10.1016/S0140-6736(10)60837-9)



Radiotherapy at time of surgery is effective.

To monitor or not to monitor

For people with type 2 diabetes, monitoring of blood glucose levels may offer limited clinical benefits – and may increase anxiety.

As well as the immediate effects of hypoglycaemia, people with diabetes are at risk of a wide range of longer-term complications, including eye and kidney damage. In type 1 diabetes, it is well-established that tight glycaemic control – keeping blood glucose levels within a narrow band – reduces the risk of complications. Regular self-monitoring of blood glucose levels is thus an important part of care. In type 2 diabetes, however, blood glucose levels fluctuate less dramatically and it is less obvious that self-monitoring is needed. Indeed, a recent randomised controlled trial found little justification for widespread self-monitoring.

The degree of glycaemic control over an extended period can also be assessed by measuring levels of glycated haemoglobin – haemoglobin chemically bonded to glucose. Raised glycated haemoglobin levels are strongly associated with higher risk of diabetic complications. If levels start to rise, clinicians can provide dietary and behavioural advice or prescribe medication.

The DiGEM trial, led by Professor Andrew Farmer at Oxford University, compared usual care alone and with additional self-monitoring. Addition of self-monitoring to measurement of glycated haemoglobin had little impact on glycaemic control, suggesting it was of limited

clinical value. In addition, self-monitoring had a negative effect on quality of life, probably because of the additional stress involved in monitoring. The study concluded that self-monitoring was not cost-effective for most patients with type 2 diabetes.

Current NICE guidelines mention self-monitoring as a possible part of the care package for people with type 2 diabetes. Patient groups and manufacturers have argued for its wider use.

Although the impact of self-monitoring was smaller than that seen in some trials, the methodology adopted by DiGEM may provide a more realistic view of its benefits. A recent systematic review in the *American Journal of Managed Care* identified an overall effect size similar to that seen in DiGEM, and singled out DiGEM's contribution. The American Diabetes Association has modified its recommendations in this area, and a review commissioned by NHS Diabetes has recommended that self-monitoring should be offered only when a clear purpose is identified. Although not a primarily economic decision, following DiGEM's advice could save the NHS around £18m a year.

Simon J, Gray A, Clarke P, Wade A, Neil A, Farmer A et al. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *BMJ* 2008;336(7654):1177–80.

Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A et al. Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial. *Health Technol Assess* 2009;13(15):iii–iv, ix–xi, 1–50.

Professor Andrew Farmer has led a trial of self-monitoring of blood glucose in type 2 diabetes.



Casting for answers

The trusty plaster cast compares favourably with newer methods of treating severe ankle sprains.

Ankle sprains are one of the most common causes of a trip to A&E – some 6000 are treated every day in the UK. Most cases are the consequence of sport or some other leisure activity. Various treatment options are available, ranging from a compression bandage costing less than £2 each to ‘ski boots’ costing hundreds of pounds, yet their relative advantages have never been formally assessed. Now, a study led by Professors Matthew Cooke and Sallie Lamb at Warwick University has found that for the most severe injuries, there is little to choose between the different options over the long term.

The CAST (Collaborative Ankle Support Trial) randomised controlled study compared four treatments: a double-layer tubular bandage; a below-the-knee plaster cast, an Aircast ankle brace and a ‘ski boot’-style support. Some 600 patients with severe sprains were followed for nine months, to assess their short-term recovery, pain experience and the longer-term consequences of treatment.

At nine months, no differences were seen between the four groups. However, the plaster cast was significantly better than the compression bandage at reducing pain in the first few months and in helping quicker recovery, so overall was the most cost-effective option. However, patients often preferred the ankle brace, which was almost as good as the cast.

With little to choose between the options from a clinical perspective, the researchers suggest that clinicians should consider patients’ preferences when deciding what approach to take, as a favoured option may accelerate recovery.

Lamb SE, Marsh JL, Hutton JL, Nakash R, Cooke MW; Collaborative Ankle Support Trial (CAST Group). Mechanical supports for acute, severe ankle sprain: a pragmatic, multicentre, randomised controlled trial. *Lancet* 2009;373(9663):575–81.

Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL et al. Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial. *Health Technol Assess* 2009;13(13):iii, ix–x, 1–121.

Traditional plaster casts are an effective option for people with severe ankle sprains.



Ever-increasing doses

Inducing tolerance to peanuts may mean children no longer live in constant fear of ingesting a potentially lethal foodstuff.

Peanut allergies can make life difficult for parents and children as peanut products such as arachis oil are widely used in foodstuffs. In severe cases, even the tiniest amount of peanut-derived material may trigger a violent immune response (anaphylaxis) that can be lethal without rapid treatment with adrenaline. A remarkable new treatment being tested by Dr Pamela Ewan and Dr Andy Clark at Cambridge University, in a project funded by the EME programme, may eliminate this fear once and for all.

During treatment, children are given gradually increasing amounts of the substance causing the allergy every day. In this case, children are given progressively larger amounts of peanut flour over a period of several weeks.

A pilot study involving 21 young people achieved remarkable early results. After tolerance was induced, all children were

able to eat at least one peanut every day with no adverse reaction – indeed, two thirds of the participants can now eat an entire handful. It is no exaggeration to say that the treatment has transformed their lives.

With the new funding, Dr Ewan and Dr Clark are undertaking a larger randomised controlled trial, with 104 peanut allergy sufferers aged between seven and 15. The team hopes to use this new trial as a template for investigating treatment of other allergies in the future, such as allergy to tree nuts. As well as testing more rigorously whether the approach is effective and safe, the Cambridge team will also aim to shed light on underlying mechanisms – as befits a project funded through the EME programme. The treatment is presumably reprogramming the immune system, yet exactly how it does so is unclear.

If mechanisms are identified, it might be possible to refine the therapy or develop pharmacological agents that have a similar effect – and it might also provide clues to the origins of other allergic responses.

Peanuts are potentially deadly to those with a severe allergy.



Why a cuff might save a kidney

Might use of a simple blood pressure cuff prolong the life of transplanted kidneys?

Since humans can live with just one kidney, living kidney donation has become a common procedure – and a vital one, as the demand for donor organs far outstrips supply. Unfortunately, one in three transplants fail within ten years, forcing patients back onto dialysis and the transplant waiting list. However, if a promising procedure being tested by Professor Raymond MacAllister and colleagues at University College London and London School of Hygiene and Tropical Medicine is successful, the number of organ failures could be significantly reduced.

A big problem in kidney transplantation is the damage caused to the kidney when it is removed and reimplanted in the recipient. Both the initial loss of oxygen supply (ischaemia) and the sudden exposure to oxygenated blood (reperfusion) can damage kidney tissue.

There may be a way to limit this damage, however. Oxygen deprivation in a localised part of the body triggers a body-wide defence response that protects against low oxygen levels. After being studied for many years in the laboratory, this phenomenon is beginning to be applied in the clinic. Professor MacAllister, for example, has found that it may help to preserve kidney function during transplantation. Crucially, the response can be provoked very simply and safely – by using a blood pressure cuff to restrict blood flow to the arm.

In an EME-funded randomised controlled trial, the effects of the cuff on donors and recipients will be tested in 400 transplants at 10 renal transplant centres in the UK and The Netherlands. Kidney function will be assessed after surgery and again a year later, to see if the procedure better preserves kidney function and, over the longer term, slows down organ deterioration. The study is also collecting molecular and cellular data, to try to identify changes that could be responsible for any protective effect.

Professor Raymond MacAllister is leading a trial of a simple technique for extending the lifespan of donated kidneys.



A route to better health?

Will a new bus scheme change people's exercise habits?

Regular exercise is known to be a route to good health, and there are growing concerns that lack of exercise is contributing to a rise in obesity and ill-health more generally. Traditionally, attempts to promote physical activity have been directed at individuals, for example through GPs. These may work for some people, but their impact is necessarily limited. Environmental changes affect large swathes of the population, and if they change people's behaviour they could have much broader impact. A new project funded through the PHR programme aims to assess what effects an innovative new public transport system in Cambridge will have on people's physical activity.

In 2010 a new busway is due to open north of Cambridge. It has been laid along a disused railway track between Cambridge and St Ives, 15 miles to the north. Modified buses will have sole use of the track, before joining the road network when they reach Cambridge. The buses will stop at major sites across Cambridge, such as its Science Park and Addenbrooke's Hospital. A cycle-path is being built alongside the busway.

Dr David Ogilvie and colleagues at the MRC Epidemiology Unit in Cambridge, University College London and the University of East Anglia are taking advantage of this unique development – the largest of its kind in the world – to see what effect it has on commuters' exercise behaviour. His team has recruited some 1100 commuters working in Cambridge, collecting information on their travel behaviour as well as demographic data and some objective measures of travel behaviour and physical activity.

Some of the commuters will be affected by the new busway, providing an opportunity to identify changes specifically related to the busway. The wealth of demographic and other data will also shed light on other factors linked to commuting and behaviour change.

Although every environmental development is different, and people's behaviour will be influenced by a unique set of factors, the Cambridge study should provide information of general value to policy-makers – such as the likely size of effects that new transport infrastructure can achieve and which factors are most likely to influence behaviour change.

Dr David Ogilvie and colleagues are exploring whether a new busway changes commuters' levels of physical activity.



A heartburning issue

Surgery beats drugs for acid reflux.

Gastroesophageal reflux disease, when stomach acids enter the oesophagus, typically causes heartburn and regurgitation, and can lead on to other more serious conditions. It is common and unpleasant but generally controllable with drugs. An alternative to long-term drug use is a surgical procedure to strengthen the valve controlling access to the stomach, which prevents backflow up the oesophagus. A recent trial suggests that this is not only clinically superior but also likely to be cost-effective.

The 'REFLUX' trial, led by Professor Adrian Grant at Aberdeen University, involved more than 800 patients and 21 hospitals across the UK. Around half of participants, who held strong views about their preferred treatment, were given their treatment of choice, while the remainder were randomly allocated to either optimised drug treatment or surgery. Patients were assessed after three and 12 months, using a quality-of-life score specifically developed for patients with reflux disease.

The study found that surgery was the more effective treatment, with the reflux quality-of-life score being significantly higher in those undergoing the surgical procedure. Notably, the greatest improvements were

seen in the group that had elected for surgery, who were most badly affected at the start of the study. Surgical complications were uncommon.

Cost-effectiveness was less easy to compare, as the costs of surgery are incurred upfront and those for medication are spread over a lifetime. An innovative cost-effectiveness model taking into account these differences also favoured surgery, with a cost per QALY gained calculated at around £2650 – well below the usual threshold used to judge cost-effectiveness.

This figure might not be so favourable if the treatment effect does not continue over the long-term, if quality of life deteriorates in those given surgery, or drugs become cheaper. A follow up to the original study, also funded by the HTA programme, will assess how patients fare over the medium term.

Epstein D, Bojke L, Sculpher MJ; REFLUX trial group. Laparoscopic fundoplication compared with medical management for gastro-oesophageal reflux disease: cost effectiveness study. *BMJ* 2009;339:b2576.

Grant AM, Wileman SM, Ramsay CR, Mowat NA, Krukowski ZH, Heading RC et al. Minimal access surgery compared with medical management for chronic gastro-oesophageal reflux disease: UK collaborative randomised trial. *BMJ* 2008;337:a2664.

Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M et al. The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial. *Health Technol Assess* 2008;12(31):1–181, iii–iv.



Surgery may be a superior intervention for people suffering from gastroesophageal reflux disease.

VenUS, VULCAN and the venous ulcer

What is the best way to treat venous leg ulcers? A series of clinical trials is helping to guide treatment in a challenging area.

Venous ulcers are common, painful and responsible for considerable healthcare costs. Typically affecting the legs of elderly people, they may take months to heal. The standard approach is to use compression bandages, which whilst effective do have some limitations, and there is an ongoing search for alternatives.

Following on from systematic reviews commissioned by the HTA programme, which revealed a very thin evidence base for the treatment of venous ulcers, 'VenUS' trials, carried out by researchers at the University of York, have examined a range of possible treatments.

VenUS II, which published its findings in 2009, examined the medicinal use of maggots to clean wounds. By far the largest study of larval therapy, VenUS II found that even though maggots cleaned wounds more quickly than simple hydrogel dressings, they did not reduce time to healing and were associated with more pain.

VenUS III, which is close to completion, is testing therapeutic ultrasound. The latest trial, VenUS IV, is comparing compression bandages with 'compression stockings' which are reusable and may be easier for patients to put on themselves – potentially benefiting patients and offering cost savings.

Finally, the VULCAN trial, led by Professor Jonathan Michaels at Sheffield University, has examined the benefits of increasingly popular silver-impregnated dressings. Silver has antimicrobial properties, so in theory could accelerate wound healing.

The VULCAN trial looked at wound healing after 12 weeks. Silver dressings, under standard compression bandages, did not significantly improve healing rates. Given their high cost, they were much less cost-effective than standard dressings. Silver dressings account for around 20–25 per cent of the total dressings budget (currently around £100 million a year), without clear evidence of their effectiveness. The VULCAN results suggest that several million pounds could be saved if their use were curtailed.

Soares MO, Iglesias CP, Bland JM, Cullum N, Dumville JC, Nelson EA et al. Cost effectiveness analysis of larval therapy for leg ulcers. *BMJ* 2009;338:b825.

Dumville JC, Worthy G, Bland JM, Cullum N, Dowson C, Iglesias C et al. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. *BMJ* 2009;338:b773.

Michaels JA, Campbell B, King B, Palfreyman SJ, Shackley P, Stevenson M. Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial). *Br J Surg* 2009;96(10):1147–56.

Michaels JA, Campbell WB, King BM, Macintyre J, Palfreyman SJ, Shackley P et al. A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: the VULCAN trial. *Health Technol Assess* 2009;13(56):1–114, iii.

Dumville JC, Worthy G, Soares MO, Bland JM, Cullum N, Dowson C et al. VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. *Health Technol Assess* 2009;13(55):1–182, iii–iv.

The VenUS trials have tested a range of methods for treatment of venous ulcers.





Aim 3 Synthesising the evidence

Considerable information about health interventions often exists in journals and other sources. This repository of information is potentially valuable, but it may be of variable quality, and being widely dispersed it is difficult for users to access and assess. Synthesising evidence is a skilled and hugely valuable activity that has become the main route by which research shapes policy.

A single large and well-designed trial may provide sufficient information to guide policy and practice, but the accumulation of numerous reliable sources can provide greater confidence. As well as providing clearer answers where the results of individual trials are in conflict or uncertain, research syntheses can also pinpoint what questions need to be answered, helping to shape future research. They can also combine clinical and cost-effectiveness analyses. Sophisticated economic modelling may even be able to indicate whether it is economically worthwhile to invest in new research to fill knowledge gaps.

A cornerstone of the NETS programme work in this area are technology assessment reviews (TARs), which are commissioned in response to the information needs of bodies such as NICE. This specialist work is carried out by seven centres across the UK. Contracts for these centres were renewed in 2010, and three new centres were appointed. The new centres will begin work in 2011.

Other parts of the NIHR Reviews Infrastructure include: the UK Cochrane Centre; the Centre for Reviews and Dissemination in York; a Cochrane Diagnostics Evaluation Unit; and a unit in Oxford for evaluating approaches to monitoring in long-term disease.

Unpicking the choices for bipolar disorder

A systematic review has helped to clarify treatment options for a complex condition.

Bipolar disorder (manic depression) is a complex and long-lasting condition, placing great strains on patients (and their families) and with the ever-present risk of suicide. Various drug options are available – including lithium, used since the 1950s – and are often used in combination. Psychotherapeutic approaches have also been tried, yet it is not clear under which circumstances the different options are suitable. A systematic review by Dr Karla Soares-Weiser and colleagues at the University of York, covering pharmacological and psychotherapeutic approaches, has provided a much clearer picture.

Bipolar disorder is characterised by periods of depression alternating with periods of elevated or highly excitable mood. Long-term treatment is necessary to prevent relapse. Lithium has been the mainstay of treatment for many years, but newer drugs are commonly used to tackle the symptoms of depression, psychosis or mania. A great deal of information exists on drug effects, and the York study aimed to systematically dissect this evidence base to provide a better guide to prescribing behaviour.

Evidence from clinical trials indicates that lithium, valproate, lamotrigine and olanzapine can help prevent relapses. For patients with mainly depressive symptoms, valproate and lithium appear to be most effective; for those with manic symptoms, olanzapine has by far the strongest effect.

Although clinicians often prescribe drugs in combination, there is no evidence that this leads to better outcomes. There is also very little evidence on the value of psychotherapies, though cognitive behavioural therapy and ‘group psychoeducation’ may be beneficial. Family therapy appears to be no more effective than individual treatment, and there is no evidence that ‘care management’ or ‘integrated group therapy’ offer any benefits.

The York team’s cost-effectiveness analyses suggest that drug treatments are cost-effective in bipolar disorder, and the choice of drug should be linked to a patient’s constellation of symptoms. Although more than 50 years old, lithium remains a cost-effective medication – and its possible contribution to reduce suicide risk may also favour its use.

The results of the analysis have been incorporated into the NHS Map of Medicine. In a fast moving field they are unlikely to be the last word on treatment but they do provide practical guidance in a complicated clinical area.

Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR. Psychosocial interventions for the prevention of relapse in bipolar disorder: systematic review of controlled trials. *Br J Psychiatry* 2008;192(1):5–11.

Beynon S, Soares-Weiser K, Woolacott N, Duffy S, Geddes JR. Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. *J Psychopharmacol* 2009;23(5):574–91.

Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technol Assess* 2007;11(39):iii–iv, ix–206.

A systematic review is clarifying for doctors the treatment options that are most suited to the symptoms experienced by bipolar disorder patients.



The bypass may be the best route

Though not without risk, weight-loss surgery is the best way for the moderately to morbidly obese to lose weight.

Obesity is one of the biggest health challenges facing the UK. If neither behaviour change nor drugs are effective (or not tolerated), various forms of bariatric surgery can be considered. A recent synthesis of research suggests that bariatric surgery is the best treatment for adults with moderate to morbid obesity where other approaches have been ineffective and, although more expensive than other treatments, it does offer good value for money.

Bariatric surgery aims to limit the passage of food through the digestive system, either by tightening a belt around the stomach (gastric banding), rerouting the small intestine to a small pouch in the stomach (gastric bypass) or 'stomach stapling' (vertical banded gastroplasty).

Although the use of these procedures has been growing in the UK, they remain relatively uncommon and many patients are turning to the private sector. With the demand for bariatric surgery likely to increase, it is important to know whether it is effective, which approaches work best and what the financial implications would be of greater use – questions addressed in a systematic review and economic evaluation carried out by Dr Joanna Picot and colleagues at Southampton Health Technology Assessments Centre.

Their analysis revealed that, for moderately and morbidly obese people, surgery is superior to other approaches. In one cohort study, weight loss in surgically treated people was maintained even after ten years while the control group who received conventional non-surgical treatment gained weight. Overall, gastric bypass was the most effective approach.

As there were no relevant economic evaluations for the UK, the Southampton team developed a new economic model to assess cost-effectiveness. This suggested that surgical approaches were cost-effective compared to non-surgical treatment for moderate to morbidly obese people, with each additional QALY costing from around £2000 to £19 000. The group does sound a note of caution, however, pointing out that surgery brings risk of adverse events, possibly even death. Too little data existed for the effectiveness of surgery in young people to be judged.

The Royal College of Surgeons has highlighted regional disparities in the provision of bariatric surgery and has suggested that the current number of procedures – around 4300 a year – is meeting only a small fraction of demand.

Picot J, Jones J, Colquitt JL, Gospodarevskaya E, Loveman E, Baxter L et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. *Health Technol Assess* 2009;13(41):1–190, 215–357, iii–iv.



A synthesis of research evidence has found that bariatric surgery is an effective method of weight loss for moderately to morbidly obese adults.

Breastfeeding neonates in intensive care

Vulnerable babies in neonatal care units could benefit more from methods proven to enhance breastfeeding.

Breastfeeding has long been known to be in an infant's best interests, providing ideal nutrition and enhancing infants' immune systems. Without breastfeeding, infants are at increased risk of a range of short-term and longer-term health impacts. Premature babies or those in neonatal care units for other reasons are at particular risk, yet successful breastfeeding may be even harder to achieve under these circumstances. The good news is that, according to a systematic review, several approaches can enhance breastfeeding of neonates.

Professor Mary Renfrew and colleagues at the University of York undertook a systematic review and economic analysis of studies on breastfeeding of babies in neonatal units, drawing on literature from a wide range of countries. Their analysis identified a range of effective interventions, including 'kangaroo care' (skin-to-skin contact between mother and infant), peer support and simultaneous breast milk

pumping. Organisational factors, such as multidisciplinary staff training and the Unicef Baby Friendly accreditation, also made a difference. The economic model showed that enhanced contact from staff trained to support breastfeeding would be cost-effective.

The neonatal care environment is undoubtedly challenging for breastfeeding. Infants may be very small and sick, mothers anxious, and medical and nursing staff hard-pressed or focused primarily on medical care. But with an increasing number of babies surviving pre-term birth, there is a growing need to ensure that they receive the nutritional, immunological and attachment benefits of breastfeeding.

Renfrew MJ, Dyson L, McCormick F, Misso K, Stenhouse E, King SE et al. Breastfeeding promotion for infants in neonatal units: a systematic review. *Child Care Health Dev* 2009; in press.

S Rice, D Craig, AF Williams, F McCormick, MJ Renfrew. An economic evaluation of enhanced staff contact for the promotion of breastfeeding for low birth weight infants. *Int J Technol Assess Health Care* (in press)

Renfrew MJ, Craig D, Dyson L, McCormick F, Rice S, King SE et al. Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis. *Health Technol Assess* 2009;13(40):1–146, iii–iv.



A systematic review has revealed that several interventions can enhance breastfeeding in paediatric intensive care.

Modernising bears fruit

Does investment in health services improve service delivery? For intensive care services at least, the answer appears to be yes.

Large sums have been invested in the NHS over the past decade or so, and it is important to know whether this investment has actually benefited patients. An analysis of data from 96 critical care units, funded through the SDO programme, has found that additional investment was associated with improved care and cost-effectiveness.

In 2000 a major shake up of critical care services was undertaken, supported by the NHS Modernisation Agency. The main aim was to integrate critical care services with other acute services in a hospital – a concept known as ‘comprehensive critical care’. At the same time funding was provided for a 35 per cent increase in the number of beds.

At the heart of the changes were the creation of 29 critical care networks covering the whole country, adoption of evidence-based ‘care bundles’ – sets of clinical guidelines covering key areas such as ventilation and infection control – and locally driven improvements. From late 2000 onwards, these changes were implemented across the NHS in England.

To assess whether they actually had any effect, Andrew Hutchings and colleagues at the London School of Hygiene and Tropical Medicine, and the Intensive Care National Audit and Research Centre, compared key factors such as survival before and after the 2000 changes, looking at nearly 350 000 admissions. In the six years after 2000, unit mortality (adjusted for the severity of cases admitted) fell on average by two per cent a year, or 11.3 per cent in total. Across a hospital as a whole, mortality for patients admitted to critical care fell by even more, 13.4 per cent. Unplanned transfers out of units because of bed shortages, which had been rising before 2000, also fell, by 11 per cent a year. Overall, the health gains suggest that the intervention has been highly cost-effective.

Because other aspects of hospital management were also changing during 2000–2006 it is not possible to say definitively that the 2000 changes were responsible for the improved outcomes (or which of the changes might have been most significant). Nevertheless, the results strongly suggest that the critical care unit modernisation has had a highly beneficial effect.

Hutchings A, Durand MA, Grieve R, Harrison D, Rowan K, Green J et al. Evaluation of modernisation of adult critical care services in England: time series and cost effectiveness analysis. *BMJ* 2009;339:b4353.



An evaluation of intensive care units has found significant improvements since 2000.

Coverage...

Professor Paul Little is Professor of Primary Care Research at the University of Southampton.

“What I think is tremendous, and a real tribute to the development of R&D funding over the last year, is the way that the funding streams plug all the gaps, so you shouldn’t get an application that falls between funding streams. There’s a place for everything, right from basic science through to the most applied.”

Multidisciplinary...

Victor Adebowale (Baron Adebowale of Thornes) is Chief Executive of Turning Point and a member of the Public Health Programme Advisory Board:

“We’ve looked at some really innovative and well-thought-through research proposals that are actually quite impressive, and when they’ve come to fruition we should see some interesting ideas about new ways of working or interventions that work.”

Children...

Monica Lakhanpaul is a consultant paediatrician and Senior Lecturer at the University of Leicester.

“Increased funding for children’s research is addressing the shortfall of good evidence. Children are a hard to reach population and it takes more money to target children especially if you want to involve children themselves in the research and not just the parents. To practise proper evidence-based medicine we need to study children specifically, acknowledge how they are different across the age range, and not just extrapolate from adult research studies.”

A place for everything, from basic science through to the most applied.





Aim 4 Disseminating the results

The results of research will have little impact unless they are disseminated. Although it is not in the remit of NETS programmes to drive the uptake of evidence-based medicine, they can help to ensure that valuable information gets to the right people in the right format at the right time.

The HTA programme publishes its own high-quality open access journal, *Health Technology Assessment*, each monograph of which provides a comprehensive record of HTA project findings. A series of supplements is devoted to single technology assessments commissioned on behalf of NICE. The NETS programmes also encourage wider dissemination of findings and liaise closely with research consumers to identify their information needs.

Research supported by the SDO and HSR programmes touches upon the most effective

ways to disseminate information through the NHS. The SDO programme also works closely with the SDO Network, part of the NHS Confederation, to disseminate findings.

The NETS programmes are an important route by which rigorous, independent research commissioned on behalf of NICE and quality-assured information can be supplied to health policy-makers. By maintaining close links with research users, the programmes can both commission research that meets users' needs and ensure that it reaches them in a suitable form.

500 not out

The *Health Technology Assessment* journal has published its 500th monograph, and its Impact Factor remains high.

While the research funded by the NETS programmes has the potential to influence healthcare provision, it will have little impact if it is not disseminated effectively. Researchers typically publish their findings in academic journals, bringing them to the attention of the wider world of researchers and clinicians, but the *Health Technology Assessment* (HTA) monograph series provides a valuable additional route for the dissemination of the complete set of findings from a study.

Around 50 HTA monographs are published each year, generally with an executive summary highlighting key findings and a full monograph providing a detailed record of the study. Unlike many primary publications, the HTA journal is entirely open access, so results are immediately accessible to all. Monographs also typically combine both effectiveness and cost-effectiveness studies,

which are often split into separate articles for other journals.

One way of judging the influence of a journal is its Impact Factor, which provides a measure of the average number of citations made to papers in the journal – the more influential a journal is, the higher its impact factor will be. The impact factor of *Health Technology Assessment* is now 6.9 (2009 data), putting the publication in the top 10 per cent of health and medical journals.

A further, more direct measure of value is how often monographs are viewed and downloaded from the HTA programme website. Between 2007 and 2009, the most popular monograph, a systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement, was viewed nearly 150 000 times, and the full suite of monographs accumulated more than 8.5 million page views.

www.hta.ac.uk/project/htapubs.asp

Health Technology Assessment monographs provide full details of research funded through the HTA programme.



Considering all the evidence

Rapid assessments can speed drug-approval processes while maintaining objective rigour.

There is an understandable drive to get new interventions assessed and approved as rapidly as possible – after all, patients may benefit and lives may be saved. On the other hand, there is still a need to ensure that new treatments are effective and represent good value for money. The new single technology assessments developed through the HTA programme on behalf of NICE have accelerated the review process but still ensure that NHS funds are wisely spent.

Technology appraisals by NICE have been informed by technology assessment reports produced by the HTA programme. While suitable for many purposes, they can be lengthy and time-consuming. With the NHS keen to have more rapid advice on newly licensed medications, the single technology assessment was developed to provide NICE with rigorous objective information in shorter time frames.

Manufacturers are obliged to provide information on their interventions' efficacy

and cost-effectiveness. It is essential, however, that these submissions are rigorously scrutinised to ensure that they provide an accurate assessment of the current clinical situation and plausible models of cost-effectiveness.

A recent single technology assessment of alitretinoin for severe hand eczema, for example, concluded that its manufacturers had accurately summarised its clinical effectiveness. However, the expert review group that conducted the appraisal identified several flaws in the manufacturer's economic model, which overestimated the likely cost-effectiveness of alitretinoin's use in the NHS. NICE ultimately recommended that alitretinoin should be prescribed when other treatments are ineffective, but was able to do so on the basis of more robust evaluation of the available evidence and with a clear idea of where additional information was needed for more accurate long-term economic assessments.

Rodgers M, Griffin S, Paulden M, Slack R, Duffy S, Ingram JR et al. Alitretinoin for severe chronic hand eczema: a NICE single technology appraisal. *Pharmacoeconomics*. 2010;28(5):351-62.



Research provided evidence of the effectiveness and cost-effectiveness of a treatment for severe hand eczema.

Building stronger bridges

Will involving management staff in research projects enhance the capacity of the NHS to take up research findings?

Commissioners and other decision-makers in the NHS are at the cutting edge of the use of information generated by research. But do managers have the background and training to make use of research evidence? One aim of a new scheme launched in 2009 by the SDO programme is to embed management staff in research projects, to enhance the capacity of managers to access and use research information effectively.

The SDO Management Fellowship scheme enables research teams that have secured funding for major projects to source additional funds so they can embed a service professional in their project. The idea is that fellows provide reciprocal benefits – enabling research to identify and respond to key issues relevant to health service management but also equip fellows with new skills and experience they can apply back in practice and pass on to colleagues.

Chris Smith, a service manager in the South West London and St George's Mental Health NHS Trust, has been seconded full-time for a year to work with Professor Christine Edwards of Kingston University and colleagues. The main project is looking at managers' use of evidence in decision-

making – when they decide they need information, where they look for it, how they access it and how they use it. As a qualified social worker with experience of management in both healthcare and social care, Mr Smith will provide valuable input from the user and management perspective, and also lead on the project's engagement and dissemination strategy.

By contrast, Sue Lawrence will continue with her 'day job' as Operations Manager, Surgical Services at Addenbrooke's Hospital in Cambridge while spending 14 months over three years advising Professor David Buchanan and colleagues at Cranfield University. The project is looking at responses to 'extreme' circumstances, when lessons might be learned from situations that have gone wrong in the health service. Given her pivotal role in ensuring the safety, quality and effectiveness of surgical services, Ms Lawrence has intimate knowledge of the factors affecting the delivery of potentially life-saving surgical treatments, and is ideally positioned to provide ongoing guidance to the research team.

These two fellows were among eight fellowships funded in 2009 and early 2010. An evaluation project was also funded to assess the impact of the Management Fellowship scheme.

Can take up of health research findings in the NHS be enhanced by involving management staff in research projects?



THE NETS Programmes

Efficacy and Mechanism Evaluation

Remit: The EME programme aims to support excellent clinical science with an ultimate view to improving health or patient care. Its remit includes clinical trials and evaluative studies – in patients – which:

- evaluate clinical efficacy of interventions (where proof of concept in humans has already been achieved);
- add significantly to our understanding of biological or behavioural mechanisms and processes;
- explore new scientific or clinical principles;
- include the development or testing of new methodologies.

Key activities in 2009/10:

- 150th preliminary application is received and 19 applications are recommended for funding.
- First patients are recruited onto EME-funded projects.
- Time taken from submission of a preliminary application to funding decision is reduced to around eight months, and a new fast-track system can allow a decision to be reached in four months in some circumstances.
- British Heart Foundation jointly funds a clinical trial, a mark of its confidence in the EME programme and the quality of its application review process.
- First examples of 'pull-through' of early phase MRC-funded clinical studies into successful EME applications (example of active translation).

The EME programme is funded by the Medical Research Council and managed by NETSCC. It was launched in April 2008 and its nominal annual budget is £15m.

Health Services Research

Remit: The ultimate aim of the HSR programme is to lead to enhanced service quality and improved patient outcomes, experience and safety through better ways of planning and providing health services.

Key activities in 2009/10:

- Board members are recruited and three Board meetings held. 100 applications are received in first call for funding.
- First projects are funded, and first outlines are short-listed for full proposals.
- Second call for funding is launched.
- Joint call for funding on public involvement in research is launched with INVOLVE.

The HSR programme is funded by the NIHR, with contributions from the Chief Scientist Office in Scotland and the National Institute for Social Care and Health Research in Wales. Its nominal budget for 2010/11 is £0.7m.

Health Technology Assessment

Remit: The HTA programme produces independent research information about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS.

Key activities in 2009/10:

- In response to H1N1 swine flu pandemic, nine projects commissioned and five researcher-led projects supported within weeks.
- Themed call on obesity is launched jointly with the PHR programme.
- First awards made following themed call in diagnostic tests and test technologies.
- Ten contracts awarded to centres of excellence for Technology Assessment Reviews, an increase in three to cope with additional demand.

- 500th Health Technology Assessment monograph is published and a supplement series launched to disseminate the results of single technology assessments.
- A second round of NIHR Clinical Trials Unit Support Funding is launched, managed by the HTA programme on behalf of NIHR.
- HTA Clinical Trials funding stream is expanded to become HTA Clinical Evaluation and Trials.

The HTA programme is funded by the NIHR, with contributions from the Chief Scientist Office in Scotland and the National Institute for Social Care and Health Research in Wales. Its nominal budget for 2010/11 is £51m.

Public Health Research

Remit: The PHR programme evaluates public health interventions, providing new knowledge on the benefits, costs, acceptability and wider impacts of non-NHS interventions intended to improve the health of the public and reduce inequalities in health.

Key activities in 2009/10:

- First project launched, linked to Royal Horticultural Society Campaign for School Gardening.
- Joint themed call on obesity is launched with the HTA programme.
- Eight projects are funded, covering a range of types of research and topic areas.
- Seven research briefs are advertised in first year of commissioned workstream.
- Stakeholder engagement programme is launched to encourage proposals and increase pool of referees.

The PHR programme is funded by the NIHR, with contributions from the Chief Scientist Office in Scotland, the National Institute for Social Care and Health Research in Wales, and Health and Social Care Research and Development, Public Health Agency, Northern Ireland. Its nominal budget for 2010/11 is £2.4m.

Service Delivery and Organisation

Remit: The SDO programme aims to improve health outcomes for people by:

- Commissioning research evidence that improves practice in relation to the organisation and delivery of healthcare.
- Building research capability and capacity amongst those who manage, organise and deliver services – improving their understanding of the research literature and how to use research evidence.

Key activities in 2009/10:

- 22 projects are commissioned in the following areas:
 - Primary care and community health services;
 - Evaluating innovations in integrating health and social care for adults and older people;
 - Research utilisation and knowledge mobilisation by healthcare managers;
 - Evaluation of a knowledge mobilisation and capacity-building initiative.
- Researcher-led workstream is launched and five projects commissioned.
- Calls are launched in the following areas:
 - Emergency planning;
 - Financial pressures;
 - Patient safety.
- 19 final reports are published.
- Portfolio comprises 79 live projects with a further 32 undergoing editorial review.

The SDO programme is funded by the NIHR, with contributions from the Chief Scientist Office in Scotland and the National Institute for Social Care and Health Research in Wales. Its nominal budget for 2010/11 is £9m.

NETS Programmes Directors and Chairs

Professor Tom Walley CBE is Director of the NETS programmes and Programme Director of the HTA programme and the EME programme. He is Professor of Clinical Pharmacology at Liverpool University and also works as a consultant physician at the Royal Liverpool University Hospital. In 2008 Professor Walley was awarded a CBE for his services to medicine.

Professor Ray Fitzpatrick is Programme Director of the HSR programme. Professor Fitzpatrick is Professor of Public Health and Primary Care at the University of Oxford. He is Chair of the Scientific Committee of the National Prevention Research Initiative and in 2008–09 he chaired the Public Health Research Board of the Office of Strategic Coordination of Health Research (OSCHR).

Professor Sallie Lamb is chair of the HTA Clinical Evaluation and Trials Board, which considers proposals from researcher-initiated open and themed calls. Professor Lamb is a Professor of Rehabilitation and Foundation Director of Warwick Clinical Trials Unit and the Kadoorie Chair of Trauma Rehabilitation at the University of Oxford. She is also an NIHR senior investigator.

Professor Catherine Law is Programme Director of the PHR programme. Professor Law is Professor of Public Health and Epidemiology at the UCL Institute of Child Health, and also an honorary consultant in public health medicine at Great Ormond Street Hospital NHS Trust. She is also Chair of the Public Health Interventions Advisory Committee at the National Institute for Health and Clinical Excellence, and is an NIHR senior investigator.

Professor Jon Nicholl was Deputy Programme Director for the HTA programme and Chair of the HTA's Commissioning Boards until March 2010. Professor Nicholl is Professor of Health Services Research, Director of Medical Care Research Unit, and Deputy Dean of the School of Health and Related Research at the University of Sheffield. He is an NIHR senior investigator.

Professor Rajesh Thakker is Chair of the EME Board. Professor Thakker is the May Professor of Medicine at the University of Oxford. He has served on several MRC grants committees, was Secretary to the Forum on Academic Medicine for the Royal College of Physicians (UK) and the Academy of Medical Royal Colleges, and a Council Member for the Society for Endocrinology. In September 2009 Professor Thakker was awarded the Founder's Award (Louis V Avioli) from the American Society for Bone and Mineral Research.

Professor Kieran Walshe is Programme Director of the SDO programme. Professor Walshe is Professor of Health Policy and Management at Manchester Business School and Director of the Institute of Health Sciences, University of Manchester.

Professor Hywel Williams is deputy director of the HTA programme. He is chair of the HTA Commissioning Board, which is responsible for assessing the scientific merit of commissioned proposals. Professor Williams is Foundation Professor of Dermato-Epidemiology at the University of Nottingham. He is an NIHR senior investigator and founded the Nottingham Clinical Trials Unit. He also chairs the Comprehensive Clinical Research Network dermatology specialty group.

Cast iron...

Anne Mackie is Director of Programmes at the UK National Screening Committee.

"Quite a lot of people don't understand what screening is. It sounds fabulously simple: you get hold of a load of people, test them and diagnose early – what could possibly be wrong with that? There aren't many places which understand that, actually, it's quite difficult to do and there's quite a lot wrong with it. The potential for doing people harm and wasting public money is huge in screening programmes. The HTA programme has a deep understanding of screening programmes and a very long relationship with the UK National Screening Committee. In terms of the monographs, we use them like bibles: if they say the cost-effectiveness looks like this, then that is cast iron for us."

Filling gaps...

Gillian Leng is Deputy Chief Executive of NICE and Chief Operating Officer for NHS Evidence.

"Our relationship with the HTA programme is important at a number of levels. Its technology appraisals are particularly important in terms of feeding into the NICE guidance programme, and as a resource for other programmes within NICE too. It works the other way too. From all our programmes we distil out needs for research and feed those back to the HTA programme, otherwise we'll still have gaps in the evidence in 10 years time."

Information...

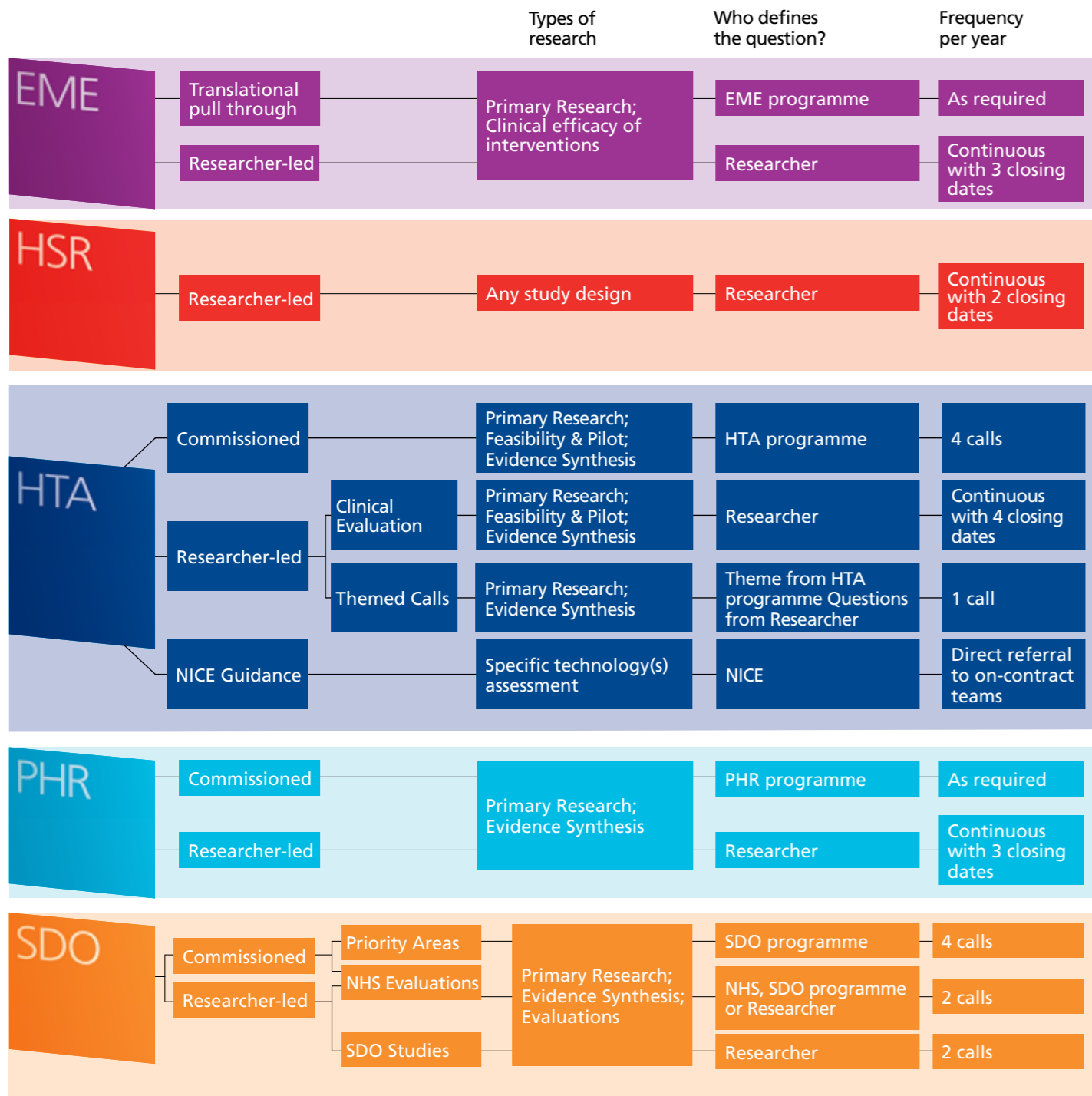
Claudia Roginski is Head of Information at Coventry Teaching PCT and an SDO Management Fellow exploring use of information in decision-making in the NHS.

"The project I'm working on with academics from Warwick looks at how people really work, what informs their decision-making, what sorts of information and experience do they draw upon, how is it all pooled? It's important to recognise the complexities of how decisions are made."

It's people who make decisions – we need to know what informs their decision-making.



Programmes managed by NETSCC



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