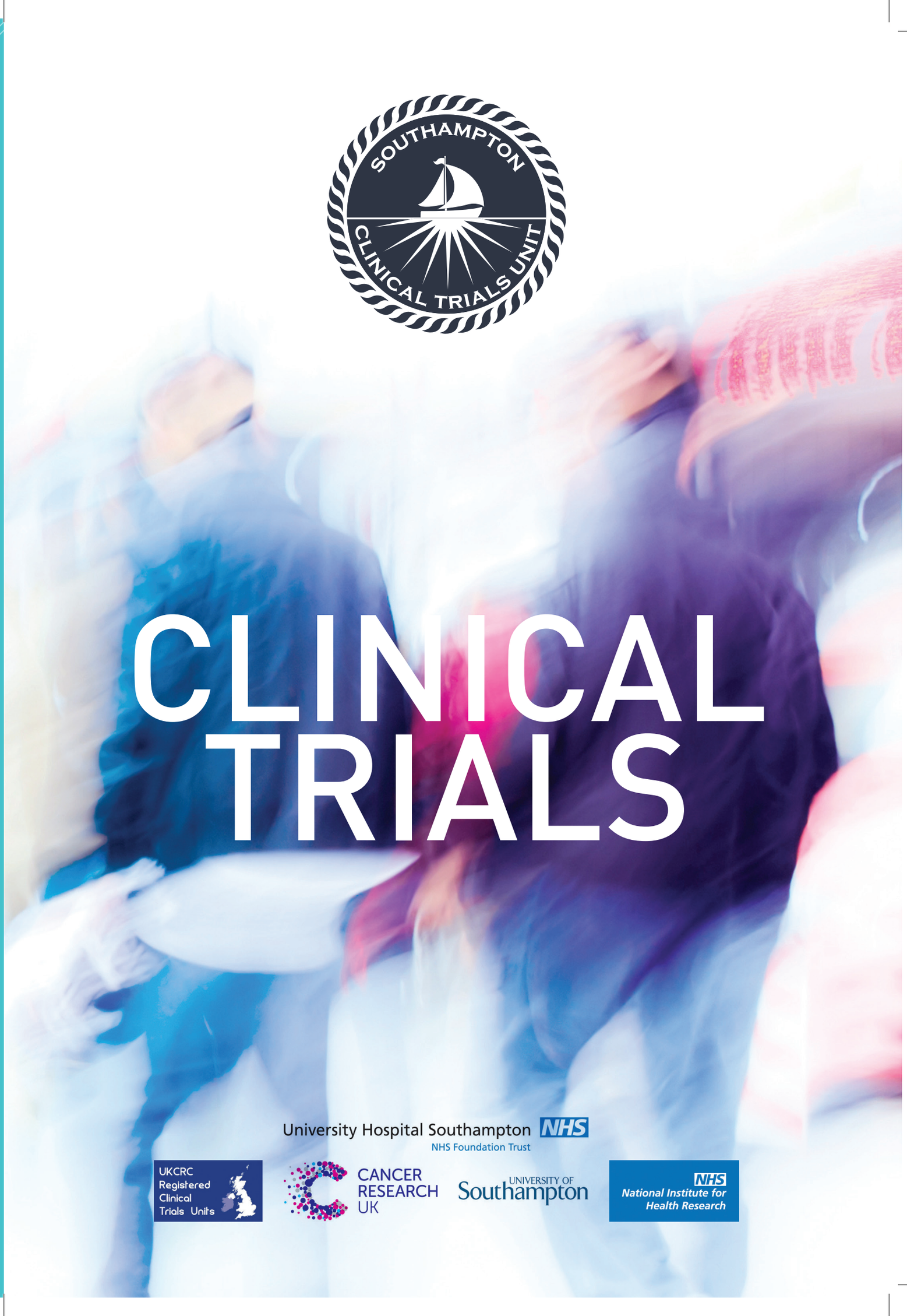

CLINICAL TRIALS

University Hospital Southampton NHS
NHS Foundation Trust

UKCRC Registered Clinical Trials Units

CANCER RESEARCH UK

UNIVERSITY OF Southampton

NHS National Institute for Health Research

THE SOUTHAMPTON CLINICAL TRIALS UNIT (SCTU)

The Southampton Clinical trials unit (SCTU) is a UKCRC registered CTU with expertise in the design, conduct and analysis of multicentre interventional clinical trials. We work in partnership with investigators alongside patient and public representatives to deliver high quality trials that will directly influence routine clinical practice.

The SCTU receives core funding from Cancer Research UK and CTU support funding from NIHR.

Our staff have expertise in developing research questions, funding proposals, trial costing and site set up. We work with our partners to ensure smooth running, timely recruiting and high quality data acquisition and analysis.

We review all applications for support against our strategic priorities which are reviewed regularly with a view to achieving a balanced portfolio.
SCTU is committed to the responsible sharing of clinical trial data and trial samples with the wider research community. Data access is administered through the SCTU Data Release Committee. Requests for data access and sharing for SCTU trials should be made by email to the SCTU Data Release Committee Coordinator at **ctu@soton.ac.uk**

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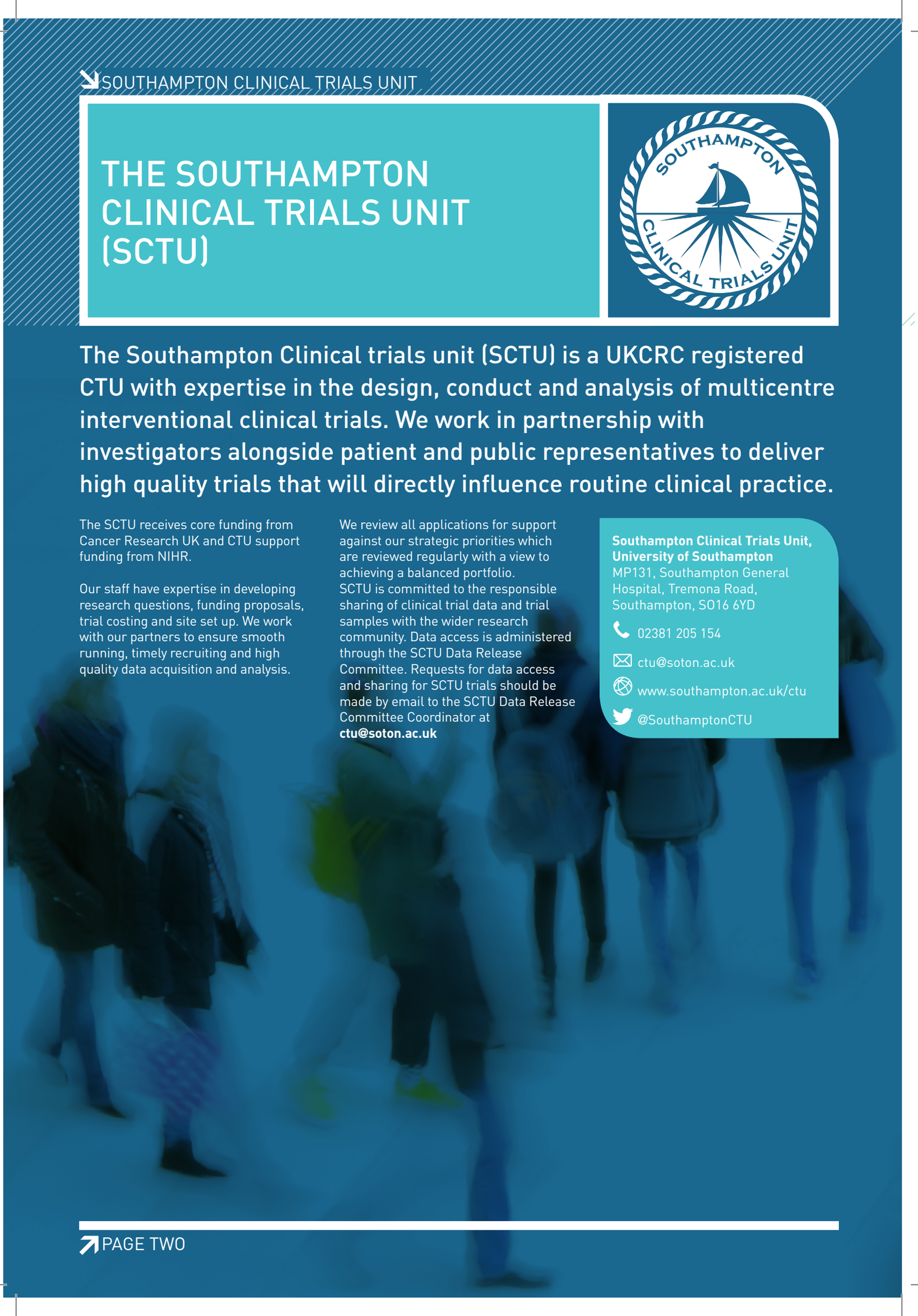

NEW TRIAL TO FIGHT CANCER CAUSED BY ASBESTOS

Patients with a hard-to-treat type of cancer are being given new hope in a new clinical trial. Researchers at the University of Southampton and the University of Leicester are trialling a drug that could boost the body's immune system to fight off mesothelioma, which can be caused by asbestos.

The trial is one of many to be conducted by the SCTU at the University of Southampton's Centre for Cancer Immunology. This is the UK's first and only centre dedicated to cancer immunology research.

BACKGROUND

Mesothelioma rates are rising. Since the late 1970s, mesothelioma incidence rates have increased almost six-fold (497 per cent increase) in Great Britain. There were around 2,700 new cases of mesothelioma in the UK in 2013 – more than seven cases diagnosed every day.

Current treatment methods include chemotherapy, radiotherapy or surgery and are mainly aimed at keeping the cancer under control.

The phase III randomised controlled trial, which is funded by Cancer Research UK and supported by Bristol Myers Squibb, will test whether nivolumab, a drug already used to successfully treat advanced melanoma and advanced kidney cancer, can be used to target mesothelioma.

It works by finding and blocking a protein called PD-1 on the surface of certain immune cells called T-cells. Blocking PD-1 activates the T-cells to find and kill cancer cells.

Professor Gareth Griffiths, the study's co-Chief Investigator from the Southampton Clinical Trials Unit at the University of Southampton, said: "The UK has one of the world's highest incidences of mesothelioma and currently there aren't many ways to treat it. Boosting the immune system by releasing killer T-cells that have previously been blocked could offer us a new way to treat more patients with this devastating disease."

The trial, which is being run in collaboration with the clinical lead Professor Dean Fennell at the University of Leicester, plans to recruit 336 patients, who have relapsed mesothelioma, across 20 UK-wide sites including Southampton and Leicester.

One person who has already benefited from using the immune system to fight mesothelioma is Mavis Nye, who was diagnosed with the disease in 2009. After various courses of treatments which failed, she joined a phase 1 immunotherapy trial to test the drug (Keytruda) on how well it blocked the PD-1 protein and enabled the body to fight off a number of cancers, including mesothelioma. After the first two years, scans revealed the tumours had decreased by 81 per cent, with three disappearing completely. Mavis is now cancer-free and spends her time raising awareness about the importance of clinical trials.

She said:

> "I was just an ordinary woman whose husband worked at the dockyards in Chatham. We didn't know what the effects of the asbestos on his clothes might be. Cancer is a terrible and devastating disease that turns everything on its head. I am so thankful that the trial I took part in worked. But it didn't work for every participant. We need more trials to help improve treatments and survival rates for cancer, and this new trial is a big step in the right direction."

STAND UP TO CANCER™

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NEW NON-INVASIVE WAY TO ASSESS PATIENTS FOR CORONARY HEART DISEASE

FORECAST (Fractional FlOw REserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of STable Chest Pain) is a large multicentre trial assessing patients presenting with chest pain at hospitals across the UK.

The FORECAST trial is comparing the way patients referred for assessment of possible angina are first assessed and then treated with a new, non-invasive technology called FFRCT. FFRCT uses the output from a computed tomography (CT) scan of the coronary arteries. This tells us whether there are narrowings or blockages in the coronary arteries, and then incorporates this into a sophisticated model to reveal whether the narrowings are causing a restriction in the blood supply to the heart. By knowing both whether there are narrowings and also whether there is a restriction in blood supply, doctors can decide whether a patient is experiencing angina and then the best way of treating them. FFRCT may save many patients from the inconvenience and risk of an invasive angiogram plus provide cost savings to the NHS. FORECAST is planning to recruit 1400 patients in about 10 centres around the UK. The trial is recruiting patients that present to a Rapid Access Chest Pain Clinic (RACPC).

All patients who are over 18 years of age, willling, able to provide written informed consent and present with the primary symptom of chest pain needing to be tested are eligible for the trial. The trial has been funded by a commercial company HeartFlow, Inc.

Heartflow Inc. is a medical technology company working on how cardiovascular disease is diagnosed and treated. The company offers HeartFlow Analysis, a non-invasive solution that enables a physician to evaluate whether a patient has significant coronary artery disease based on anatomy and physiology. Its HeartFlow Analysis is available in the United States, Europe, and Japan.

The trial intends to compare whether routine FFRCT is superior in terms of resource ultilisation at 9 months, when compared to routine clinical pathway algorithms recommended by NICE CG95.

Professor Nick Curzen, Consultant Cardiologist at University Hospital Southampton NHS Foundation Trust and Chief Investigator for the FORECAST trial said:

> “FFRCT if it proves effective may save many patients from the inconvenience and risk of an invasive angiogram plus provide cost savings to the NHS.”

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TREATMENTS FOR ADULT FEMALE ACNE

Many adults live with acne for years, and the most common treatment is antibiotics. But the prolific use of antibiotics and the problem of antibiotic resistance means that this is far from ideal.

The SAFA (Spironolactone for Adult Female Acne) trial is seeking to find a solution. Spironolactone helps to reduce blood pressure but it also has an impact on hormones. It's the hormonal effect that potentially makes it useful for treating acne. The SAFA trial is being funded by the National Institute for Health Research and participants will be women over the age of 18. They will be randomised so some will take spironolactone and others will take a placebo.

The SAFA trial is being managed from the Southampton Clinical Trials Unit in collaboration with the Primary Care and Population Sciences Unit, Faculty of Medicine and is sponsored by the University of Southampton.

Dr Miriam Santer, GP and Associate Professor in Primary Care Research, is the Chief Investigator for the study. Miriam, has previously led research that has focused on skin conditions and helping people to manage them. She said: "Spironolactone is a pill that is widely used for treating high blood pressure. Some dermatologists use it to treat acne, especially in the United States, but there have hardly been any trials conducted around this, and the biggest trial to date only involved 50 participants. So there is very little evidence to help support a decision on whether it should be used to treat acne."

Over 400 participants will be recruited from Southampton and Portsmouth hospitals and through GP practices around the country. Recruitment will take place over 18 months, with each participant taking the drug or placebo for six months.

The results from the study will be reported in three to four years' time, and forms part of the University's NAMRIP (Network on Antimicrobial Resistance and Infection Prevention trials) trial portfolio.

Dr Miriam Santer, Chief Investigator for the trial said:

> "A very visible skin disorder such as adult acne has a multitude of psychological and social effects, causing depression and low self-esteem and even going as far as to impact on employment and relationships."

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FOCUSING ON BREATHING RETRAINING FOR ASTHMA. THE BREATHING FREELY STUDY (BREATHE)

Despite effective pharmacotherapy, asthma continues to impair quality of life for most patients. Non-pharmacological approaches, including breathing retraining, are therefore of great interest to patients. However, clinicians rarely advocate breathing retraining and access to this intervention is restricted for most patients due to the limited availability of suitable physiotherapists and poor integration of breathing retraining into standard care. The BREATHE study was carried out to assess the effectiveness of a digital self-guided breathing retraining intervention.

In the Breathe Study (funded by the National Institute for Health Research), patients were randomly allocated to either a digital (DVD plus booklet) or face-to-face physiotherapy programme, or usual care.

Both the digital (DVD plus booklet) and face-to-face physiotherapy programmes improved patients' asthma-related quality of life scores (over 12 months) compared with those receiving usual care, with improvements that are comparable to those achieved by increasing medication.

The NHS healthcare costs were lower for both breathing retraining groups than for the usual care control group, and were lowest when access was provided digitally. Savings made by delivering the programme in this way outweigh any technology provision costs.

The use of DVDs has declined since the inception of the study, with a corresponding growth in online and streamed sources for provision of digital information and entertainment. Accordingly, to make this intervention accessible to clinicians, researchers, and people with asthma, the BREATHE team have made the content of the DVD and the supporting booklet freely available online through the Breathe study website.

www.breathestudy.co.uk

The low cost of providing an internet based intervention, the ease of access of content and the absence of adverse outcomes using such approaches indicate that this evidencebased non-pharmacological intervention can now be offered to people with asthma with persisting quality-of-life impairment despite current asthma medication.

There is a need to stress to patients that this intervention is in addition to, not instead of, current medication, and that it does not cure asthma, but rather is a means to improve quality of life.

Professor Anne Bruton, trial Chief Investigator, said:

> "Developed by an experienced team of GPs, physiotherapists, psychologists and patients at the University of Southampton, Breathing Freely was shown to improve the lives of people with asthma, in the Breathe Study. The Breathe Study is now finished but you can try Breathing Freely yourself through the links on the website - it's completely free."

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ENHANCED PREOPERATIVE DIABETES MANAGEMENT TO IMPROVE THE OUTCOMES OF ELECTIVE SURGERY FOR DIABETICS

Improving the outcomes for patients with diabetes mellitus following cardiac surgery.

There are around 4 million people living with diagnosed and undiagnosed diabetes mellitus (DM) in the UK. Since 1996, the number of people diagnosed with DM has increased from 1.4 million to around 3.5 million. Diabetes increases the risk of cardiovascular disease by approximately 2 fold after adjustment for other cardiovascular risk factors. As a result ischaemic heart disease is by far the leading cause of death in people with DM accounting for approximately 2/3rd of all deaths in those aged over 65 years. Coronary heart disease tends to be more diffuse and progresses more rapidly in people with DM which may explain why up to 35% of those presenting for elective cardiac revascularisation have DM. Poor glycaemic control also increases the risk of wound and chest infections, renal impairment and death, especially following cardiac surgery.

This trial called OCTOPUS (funded by the National Institute for Health Research) will address whether a preoperative outpatient non-doctor delivered intervention to improve glycaemic control can improve cardiac surgical outcomes for diabetic patients.

The increasing number of people with DM will increase the demand for cardiac surgery in the future. These patients have longer lengths of hospital stay and higher readmission rates, placing a large financial burden on the NHS. If the preoperative intervention is successful in improving glycaemic control, this may reduce the complication rates for such surgeries and improve outcomes for these diabetic patients.

Professor Richard Holt, Professor in Diabetes and Endocrinology and Chief Investigator for the trial said:

> “We know that people with diabetes tend to make a slower recovery after surgery and many of the reasons behind this could be addressed prior to surgery. We hope that by introducing people with diabetes awaiting cardiac surgery to a specialist diabetes team we can help prepare them better for surgery. If our trial confirms this, we will be able to make the in-patient stay of people with diabetes easier and safer.”

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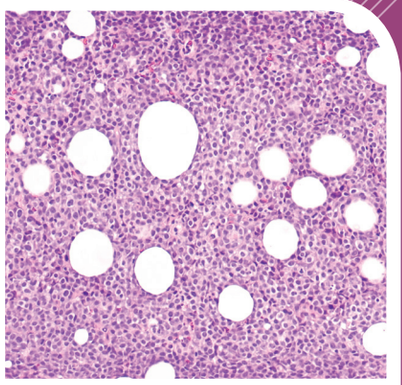
EXPERIMENTAL DRUG TRIAL SEEKS TO IMPROVE TREATMENT FOR LYMPHOMA



Patients with a common type of fast-growing cancer are being given fresh hope in a new clinical trial. Scientists at the University of Southampton are, for the first time, to trial a new experimental drug, in combination with immunochemotherapy, in certain patients with diffuse large B-cell lymphoma (DLBCL).

DLBCL is the most common type of fast-growing non-Hodgkin lymphoma. For many people, the standard treatment, called R-CHOP, uses a combination of an immunotherapy called rituximab and four chemotherapy drugs to find and destroy lymphoma cells. However sometimes DLBCL does not go away, or comes back after a period of remission.

Researchers at the University of Southampton want to find out whether a new protein inhibitor called acalabrutinib improves patient response to standard treatments. Acalabrutinib is being developed by Acerta Pharma, a member of the AstraZeneca group.

The ACCEPT trial, which has launched at seven centres across the country and is being funded by Acerta Pharma, will be managed by the Southampton Clinical Trials Unit, and will for the first time combine acalabrutinib with R-CHOP.

The first phase of the trial will help determine a safe and tolerable dose of the drug. Patients will receive multiple low doses of acalabrutinib, while samples of blood and other fluids, collected at various time points, are analysed for information on how the body processes the drug in combination with R-CHOP.

The subsequent phase will evaluate whether this treatment combination is effective at treating DLBCL and preventing its return.

Dr Andrew Davies, lead researcher on the trial and associate professor and consultant in medical oncology at the University of Southampton, said: "For some lymphoma patients standard treatments are not effective, so we urgently need trials like this to help more people survive their disease.

Results from previous trials that use acalabrutinib to fight other blood cancers have been very promising. This new and unique drug combination will attack the cancer from two sides. Not only will it mark the cancer cells so the immune system can find them and kill them, but it will also prevent the activity of key proteins that play an important role in the spread and survival of malignant B cells. We believe this new combination will benefit patients in addition to standard treatment."

ACCEPT is the first clinical trial to be run as part of the Precision Medicine for Aggressive Lymphoma Consortium (PMAL). Gene expression data gathered as part of this trial will be used by PMAL to improve diagnosis and treatment for lymphoma. It will contribute to a sophisticated database which could one day match patients to targeted therapies based on genetic profiling.

Professor Peter Johnson, director of the Southampton Cancer Research UK Centre, said:

> "This trial is exciting because it uses a new targeted cancer drug to switch off key signals in lymphoma cells, and at the same time we will be able to collect information about whether this is a good approach for more patients in the future."

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IMMUNE-BOOSTING ANTIBODY COMBINATION COULD IMPROVE LYMPHOMA SURVIVAL

Combining two different immunotherapy treatments could dramatically improve lymphoma survival.

In 2016 researchers from the University of Southampton tested different combinations of antibodies in the lab to see how they interact with each other, and what effect this has on how the immune system fights cancer.

They found one combination – anti-CD27 and anti-CD20 – greatly increased life expectancy in mice with cancer. Whilst most of the mice treated with one of the antibodies did not survive beyond 80 days, nearly all mice given both antibodies survived beyond 100 days.

When combined, the researchers found the antibodies enhance the number and ability of the body's own defence cells to destroy cancer cells.

As a direct result of this study, this antibody combination has rapidly moved into a clinical trial (RiVa) involving four hospitals in England, including at Southampton General Hospital.

Dr Sean Lim, a Cancer Research UK clinician scientist at the University of Southampton, said: "It's very exciting to see that this drug combination has an impact on survival of mice with lymphoma. Improvements in treatment for patients are urgently required. This clinical trial will allow us to see whether the promising research will translate into benefit for patients."

The trial will be one of many run by the Southampton Clinical Trials Unit out of the University of Southampton's Centre for Cancer Immunology, which is the UK's first and only centre dedicated to cancer immunology research. The trial is jointly funded by CRUK and CELLDEX Ltd.

Professor Karen Vousden, Cancer Research UK's chief scientist, said:

> "This study greatly increases our understanding of how different immunotherapies can work together to improve the way we treat lymphoma. By testing this approach in a clinical trial we will see if this promising research will translate into benefit for patients."

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SPIRE - NEW TRIAL TO TEST DRUG FOR RESISTANT BLADDER CANCER IS LAUNCHED

"Studying drug resistance in cancer helps us get one step ahead of the disease, allowing us to target its defences. We've seen a lot of drug combinations in the news recently and we hope that this approach will help in bladder cancer where there are few options for patients." **Nigel Blackburn, CRUK's director of drug development**

A clinical trial to test a drug which may stop bladder cancers becoming resistant to chemotherapy is being run by the Southampton Clinical Trials Unit.

The new phase I/II trial – called SPIRE – will test a drug called guadecitabine (SGI-110) in combination with chemotherapy to see if it can treat the disease and stop patients becoming resistant.

The first part of the trial open in centres across the UK – will give small doses of guadecitabine to between three and 36 patients with advanced solid tumours, including bladder, lung, stomach and oesophageal cancers, to ensure the drug is safe and to find the most effective dose.

The drug will then be tested in 20 bladder cancer patients to see how well it works against the cancer.

Guadecitabine is a type of DNA methyltransferase inhibitor – a drug that blocks molecules that can modify DNA. In cancer these molecules turn off genes that should be on, causing resistance to chemotherapy.

The researchers hope that giving the drug alongside the chemotherapy will block this resistance.

Each year around 10,400 people are diagnosed with bladder cancer in the UK and more than 5,200 people die from the disease.

Dr Simon Crabb, trial Chief Investigator, said:

> "Advanced bladder cancer can be a difficult disease to treat and we desperately need to improve our treatment options. Our trial offers a new approach to tackling resistant bladder cancers and there's promising lab research to suggest it might benefit patients. We hope our trial is a success and prompts larger clinical trials to evaluate the benefits of this approach for the thousands of bladder cancer patients in the UK."

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SURVIVAL FOR YOUNG WOMEN TREATED FOR BREAST CANCER IS THE SAME WHETHER OR NOT THEY CARRY A BRCA MUTATION

After treatment, young women diagnosed with breast cancer who carry a BRCA mutation have the same chances of survival as women without the mutation, according to a prospective cohort study run from the SCTU.

BRCA mutations occur in either the BRCA1 or BRCA2 gene, and are inherited. These mutations place women at a greater risk of breast and ovarian cancers, with 45-90 per cent of women with the mutation developing breast cancer during their lifetime, compared to roughly 12.5 per cent of women developing breast cancer in their lifetime overall in the UK.

The POSH study, published in The Lancet Oncology journal, recruited young women with breast cancer between the years 2000 and 2008, when BRCA testing and risk-reducing surgery were not routine for early breast cancer. The paper looks at survival following treatment for the initial breast cancer diagnosed only, as previous evidence on whether carrying these types of mutation affects a woman's cancer prognosis has been mixed.

Now, after first cancer diagnosis and treatment, women with early breast cancer and BRCA mutations are often offered risk-reducing surgery (such as a double mastectomy, or surgery to remove the ovaries and fallopian tubes) to help reduce the risk of new primary breast or ovarian cancers.

"Our study is the largest of its kind, and our findings suggest that younger women with breast cancer who have a BRCA mutation have similar survival to women who do not carry the mutation after receiving treatment," says Professor Diana Eccles, Head of Cancer Sciences at the University of Southampton.

"Women diagnosed with early breast cancer who carry a BRCA mutation are often offered double mastectomies soon after their diagnosis or chemotherapy treatment, however, our findings suggest that this surgery does not have to be immediately undertaken along with the other treatment. In the longer term, risk-reducing surgery should be discussed as an option for BRCA1 mutation carriers in particular, to minimise their future risk of developing a new breast or ovarian cancer. Decisions about timing of additional surgery to reduce future cancer risks should take into account patient prognosis after their first cancer, and their personal preferences."

The study involved 127 hospitals across the UK and included 2733 women aged 18-40 years who had recently been diagnosed with breast cancer for the first time.

The women were recruited between January 2000 and January 2008, and their medical records were tracked for an average of 8.2 years to gain information about their diagnosis, treatment, whether their cancer came back, or if they died.

During this time, out of the 2733 women, there were 678 deaths, including 651 deaths from breast cancer, 18 from other cancers, and nine from other causes.

All women included in the study were tested for BRCA mutations, and 338 (12 per cent) carried one – including 201 women with a mutation in the BRCA1 gene, and 137 with a mutation in the BRCA2 gene.

The study found that there was no difference in overall survival two, five or 10 years after diagnosis for women with and without a BRCA mutation.

Tom Maishman, Lead Statistical Methodologist of the POSH study, said:

> "This study provides us with unique insight into the factors affecting survival in young women with breast cancer, and helps us determine the best treatment approaches to use for these patients."

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PROFESSOR GARETH GRIFFITHS

BSC, MSC, PHD

PROFESSOR OF CLINICAL TRIALS, DIRECTOR OF THE SOUTHAMPTON CLINICAL TRIALS UNIT

Professor Gareth Griffiths is a Professor of Clinical Trials at the University of Southampton.

Professor Gareth Griffiths was appointed to the Chair of Clinical Trials and Director of the Southampton Clinical Trials Unit in July 2014. Having graduated with a BSc in Biological Sciences (joint statistics and biology) at Reading University, a MSc in Statistics in applications in Medicine at Southampton University and later a Phd in bladder cancer clinical trials at Cardiff University Gareth has spent the majority of his career in the area of clinical trials. He has held the position of senior statistician/scientific lead at the MRC Clinical Trials Unit, London, Director of the National Institute for Social Care and Health Research (NISCHR - Wales) Cancer Registered Research Group and Director and founder of the Wales Cancer Trials Unit in Cardiff before his current appointment at Southampton University. Professor Griffiths is the Director of the UKCRC registered Southampton Clinical Trials Unit (SCTU) which is based within the Faculty of Medicine. Southampton CTU is Cancer Research UK (CRUK) core funded and receives National Institute for Health Research (NIHR) clinical trials unit support funding.

DR ANDREW COOK

MBBS, MPH

CONSULTANT IN PUBLIC HEALTH MEDICINE & FELLOW IN HEALTH TECHNOLOGY ASSESSMENT, ASSOCIATE DIRECTOR OF SOUTHAMPTON CLINICAL TRIALS UNIT

Dr Andrew Cook is a Consultant in Public Health Medicine and Fellow in Health Technology Assessment at the University of Southampton.

Dr Cook works with both the Southampton Clinical Trials Unit, and the NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC). He graduated in Medicine from St Georges Hospital Medical School at the University of London, then after working in Emergency Medicine, Internal Medicine, and Psychiatry, training in Public Health Medicine in the West Midlands. While training he gained a Master of Public Health degree from the University of Birmingham. Since joining the University of Southampton he has been Director of Service Delivery and Organisation, and Director of Public Health Research, at NETSCC. He was Director of the Southampton Health Technology Assessments Centre until August 2015, before starting with the Clinical Trials Unit. He also has roles as a consultant advisor at NETSCC, leading on surgery and interventional procedures for the NIHR Health Technology Assessment programme, and providing clinical and scientific advice to the NIHR Public Health Research programme.

DR SIMON CRABB

BSC, MBBS, MRCP, PHD

ASSOCIATE PROFESSOR IN MEDICAL ONCOLOGY, ASSOCIATE CLINICAL DIRECTOR OF SOUTHAMPTON CLINICAL TRIALS UNIT

Dr Simon Crabb is an Associate Professor in Medical Oncology at the University of Southampton.

Dr Crabb graduated in medicine from St George's Hospital Medical School, London in 1996. He joined the University of Southampton in 2002 as a Cancer Research UK Clinical Research Fellow and was awarded his PhD in 2006 for work involving novel histone deacetylase inhibitors. Following a Clinical Research Fellowship at the BC Cancer Agency in Vancouver, he returned to the Cancer Sciences Unit in Southampton where he now works as an Associate Professor and Honorary Consultant in Medical Oncology.

Dr Crabb's research interests are in the development of novel therapeutic strategies for bladder cancer and prostate cancer, epigenetic therapeutic agents and mechanisms of systemic treatment resistance. He is an active clinical and translational researcher who leads and collaborates on a number of early phase clinical trials for genitourinary cancers.