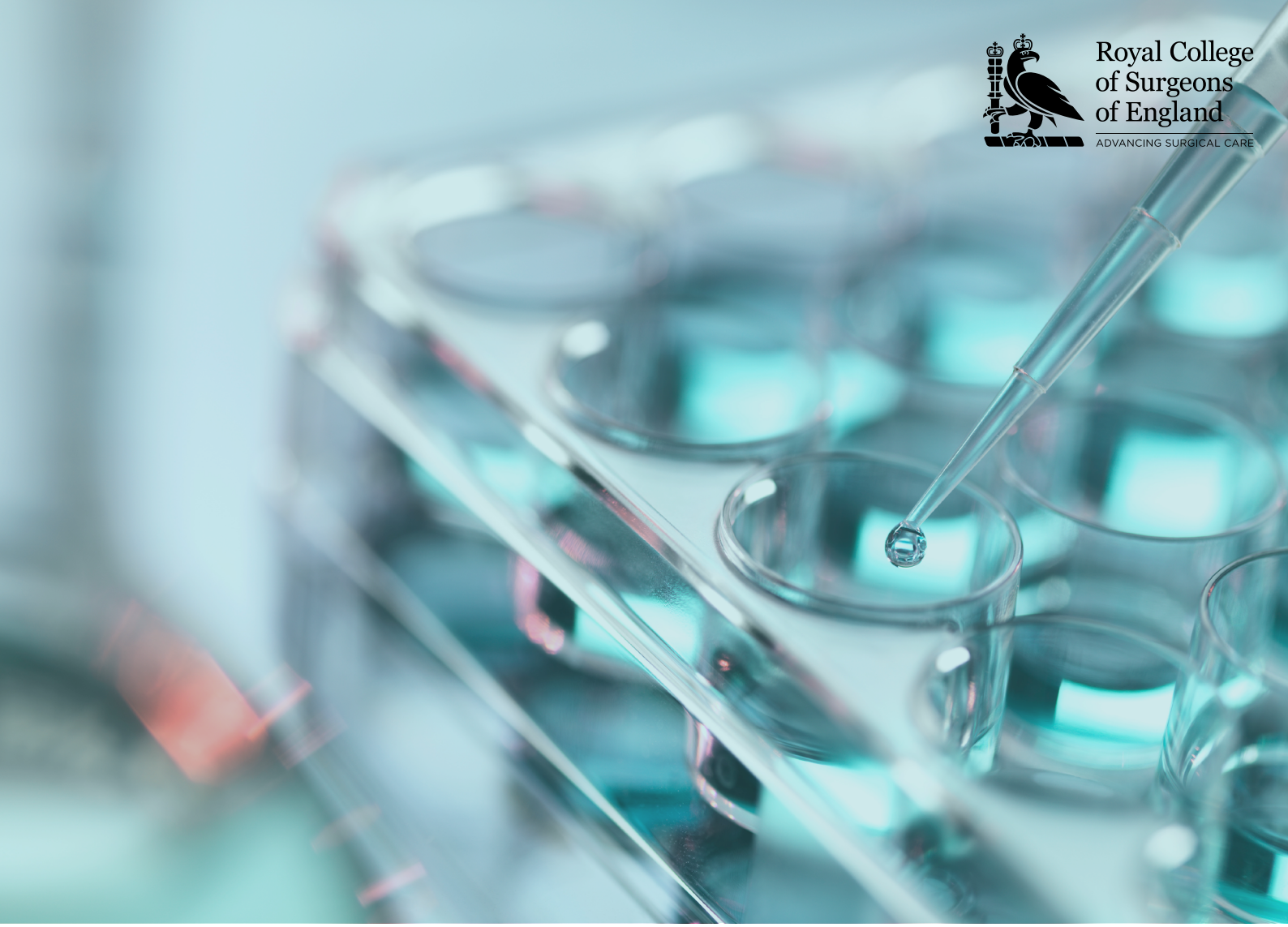

Royal College of Surgeons of England
ADVANCING SURGICAL CARE

Impact of the Royal College of Surgeons of England Clinical Trials Initiative

The Royal College of Surgeons of England Clinical Research Initiative: 10 years of progress

Collaborative authorship: RCS England Clinical Research Initiative

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Authors

Prof Peter Hutchinson
Prof Tom Pinkney
Midhun Mohan
Murat Akkulak
Angelos Kolias
Ralph Tomlinson
Prof David Beard
Prof Linda Orr
Prof Dion Morton

RCS England Chairs
Prof Joy Adamson
Prof David Beard
Prof Michael Douek
Prof Rob Hinchliffe
Prof David Jayne
Prof Michael D Jenkinson
Prof Cliona Kirwan
Prof Amar Rangan
Prof Tom Pinkney

RCS England Surgical Trials Centre Directors Past and Present
Prof Jane Blazeby
Prof Julia Brown
Prof Nigel Bundred
Prof Peter Brocklehurst
Prof Marion Campbell
Prof Andy Carr
Julie Croft
Prof Freddie Hamdy
Prof Paula Ghaneh
Prof Iain Hutchison
Prof Pam Kearns
Prof Graeme MacLennan
Dr Laura Magill
Prof Catriona McDaid
Prof Gavin Murphy
Prof James N'Dow
Prof Craig Ramsay
Prof Chris Rogers
Prof Deborah Stocken
Prof David Torgerson

Current RCS England SSLs
Prof Matt Bown
Mr Dan Carradice
Mr Filipe Correia-Martins
Prof Peter Friend
Mr Matt Gardiner
Prof Xavier Griffin
Prof Paul Baker
Mr Nigel Hall
Mr Douglas Hammond
Prof Michael D Jenkinson
Mr Robert Jones
Mr Stuart McIntosh
Prof Caroline Moore
Prof Susan Moug
Prof Gavin Murphy
Mr James O'Hara
Prof Daniel Perry
Ms Shelley Potter
Mr Dimitrios Pournaras
Ms Emma Reay
Prof Keith Roberts
Mr George Smith
Prof Tim Underwood
Mr Dale Vimalachandran
Ms Louise Wan

Past RCS England SSLs
Mr Simon Bach
Prof Jane Blazeby
Prof Ian Chetter
Prof Matt Costa
Prof Adele Francis
Prof Peter Hutchinson
Prof Abhilash Jain
Prof Dae Kim
Prof Jim McCaul
Mr Sam McClinton
Prof Amar Rangan
Prof Anne Schilder
Prof David Taggart

Introduction

During the previous century, some argued that surgical clinical research was faltering. In 1996, Richard Horton's now infamous editorial 'Surgical research or comic opera: questions, but few answers' was critical of surgical research. He quoted the words of medical statistician Major Greenwood from 1923: "I should like to shame (surgeons) out of the comic opera performances which they suppose are statistics of operations". Horton stated that, in surgery journals, 7% of papers reported data from randomised controlled trials (RCTs), and case series were the most common type of manuscript. He concluded that logic insists that a large proportion of the surgical literature is of questionable value and proposed that only when the quality of publications in the surgical literature has improved will surgeons reasonably be able to rebut the charge that as much as half of the research they undertake is misconceived.

Richard Horton was certainly harsh but was he fair? Perhaps an analysis of the literature would have shown the same criticisms were applicable to other specialties. However, there were issues in terms of surgical research. It could be argued that, historically, surgeons focussed on surgical competence, training and management rather than research, and funding agencies focussed on basic science and translational research. In 2008–2009, the combined spend on surgical research was less than 2% of the total research budget, yet 30% of NHS patients received surgical care.

However, 10 years ago this began to change. Surgical research entered a new era, with a dramatic increase in the delivery of trials, specifically RCTs. The infrastructure underpinning this evolution was threefold. Firstly, the birth of the National Institute for Health and Care Research (NIHR); the NIHR has played a fundamental role both in terms of access to funding, particularly through the Efficacy and Mechanism Evaluation (EME) and Health Technology Assessment (HTA) funding schemes, and delivery of research via the Clinical Research Network (CRN) and through NIHR infrastructure in NHS Trusts to deliver trials. Secondly, the formation of the Royal College of Surgeons of England (RCS England) Clinical Research Initiative, and thirdly a growth in methods suitable for the design and delivery of surgical trials, much of which was funded by investment into the Medical Research Council (MRC) initiative 'Hubs for Trials Methodology Research' in 2010.[1] More recently, the Research Excellence Framework has changed by increasing the emphasis towards impact that surgical research can certainly deliver.

A new surgical culture that places emphasis on conducting high-quality clinical research to advance patient care is now firmly established in the UK. In turn, this has led to a growth in surgical research output. There is now a substantial cohort of surgeons determined to deliver high quality research; importantly, this includes not just academic consultants but also NHS consultants, who form the majority of the surgical workforce in the UK. The role of trainees, particularly the major impact of trainee collaboratives, cannot be overstated. Moreover, collaboration with other specialties and methodologists has been crucial. Horton had stated in his editorial that "to retain their academic reputation surgeons must find imaginative ways to collaborate with epidemiologists to improve the design of the case series and to plan randomised trials". We have added to that trial methodologists, statisticians, health economists, database programmers, qualitative researchers and patient representatives. The role of the Clinical Trials Units (CTUs) and the NIHR CRN infrastructure has also been critical in the successful delivery of surgical trials.

RCS England Clinical Research Initiative

The RCS England Clinical Research Initiative was established in 2013. It was the vision of Presidents Professor Sir Norman Williams and Professor Derek Alderson, and the first Director of Clinical Research, Professor Dion Morton. The initiative comprises three components: i) the Surgical Specialty Leads (SSLs) and trainee associate SSLs, ii) Chairs in Surgical Trials and iii) Surgical Trials Centres. RCS England works closely with the NIHR both in terms of funding (e.g. via the NIHR HTA Prioritisation committee) and delivery of research via the NIHR CRN. The generous support of our partners, Rosetrees Trust among others, was crucial in both initiating and growing the initiative.

Since 2011, the number of open NIHR portfolio trials has increased from 101 to 391. Trials run by Surgical Trials Centres have increased from 11 to 66 and Surgical Trials Centres have now recruited over 50,000 patients into trials. In total, since 2011, in collaboration with the NIHR, over 400,000 patients have been entered into surgical trials and over 1,000 surgical trials in the NIHR CRN portfolio (Tables 1 and 2 and Figure 1).

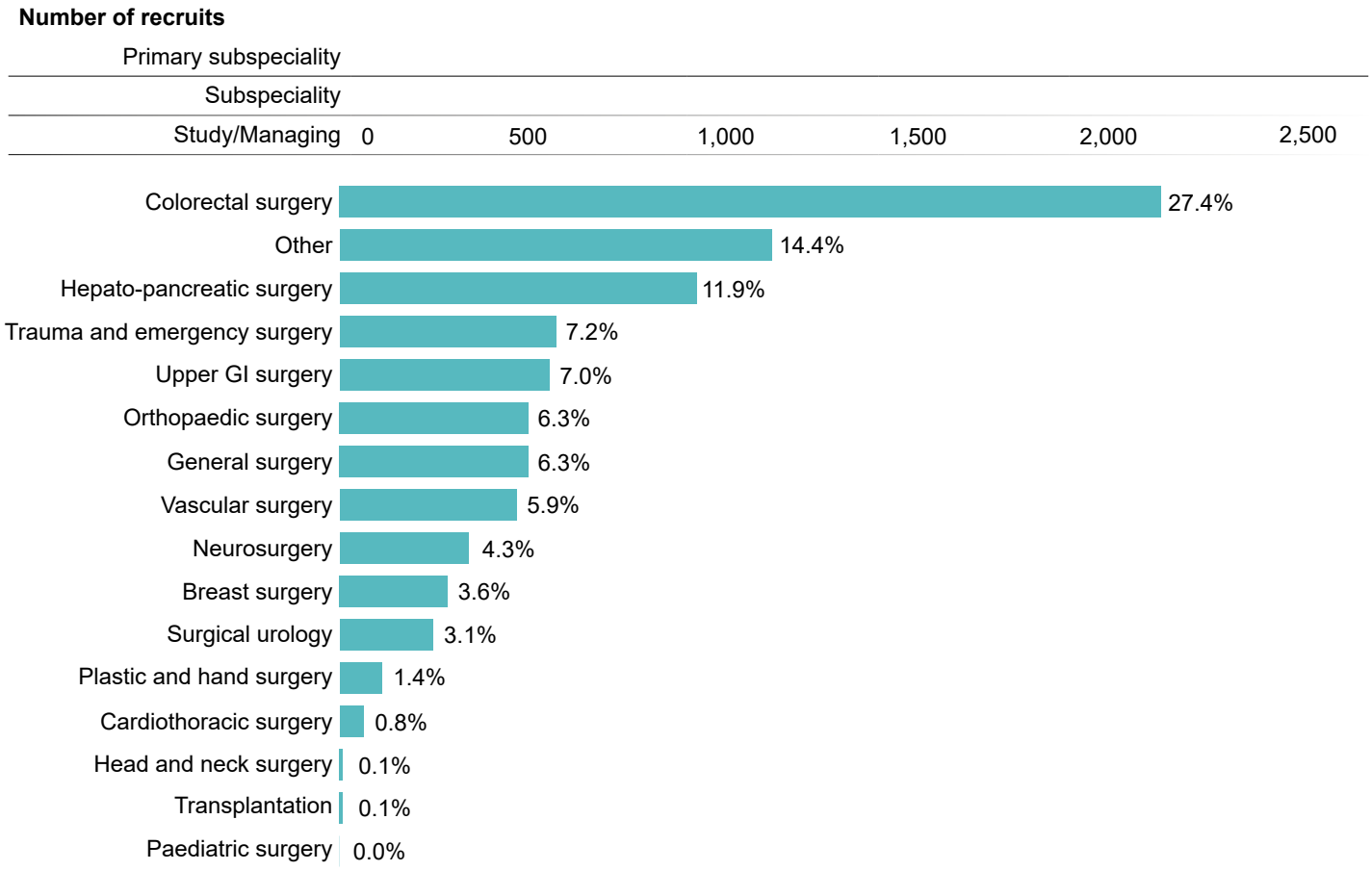
Table 1 Recruitment into surgical trials (Datacut 5 November 2021, acknowledgement: NIHR CRN)

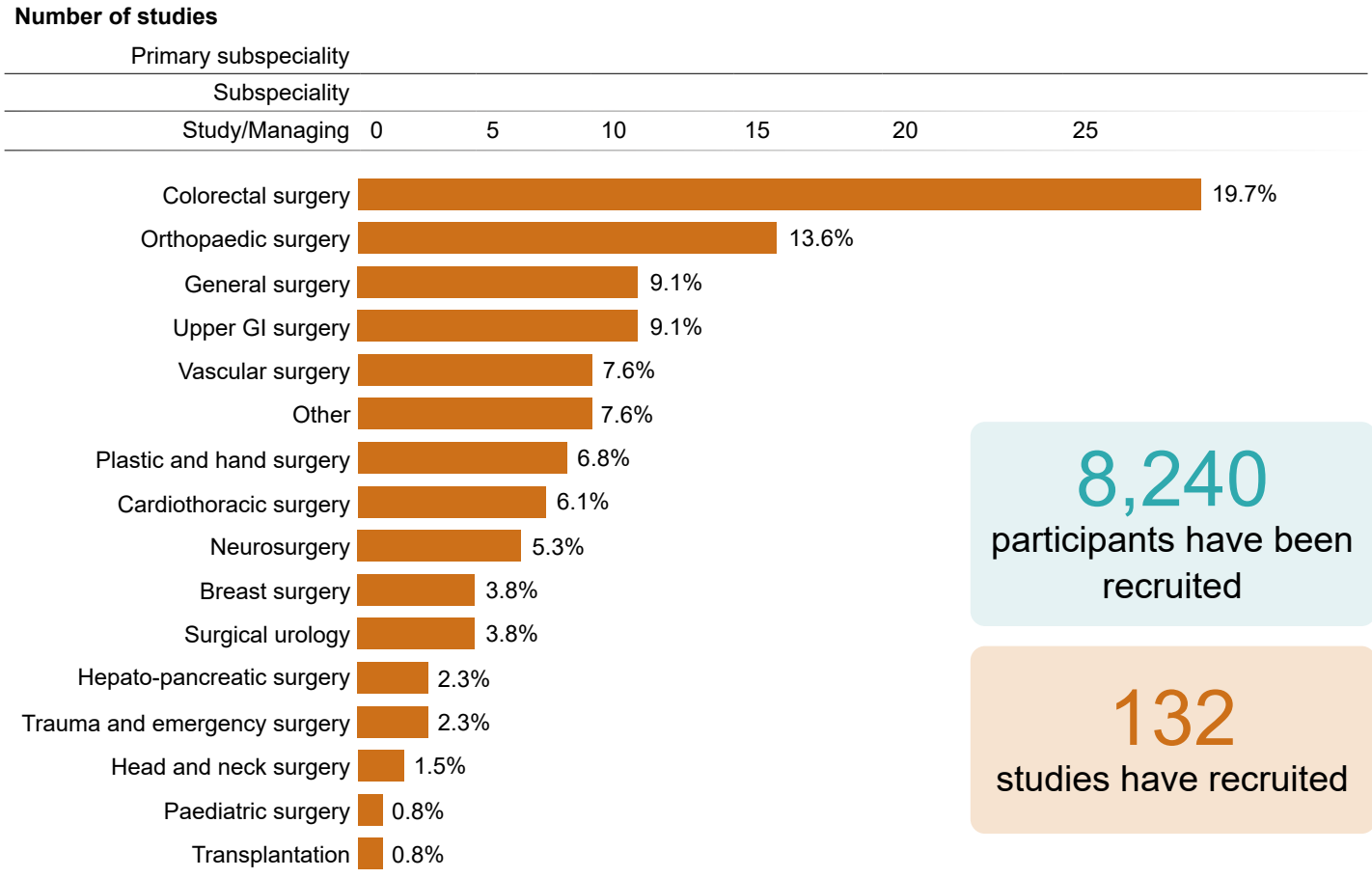
Recruitment year (FY)	Commercial	Noncommercial	Total
2010–2011	243	11,694	11,937
2011–2012	367	16,927	17,294
2012–2013	731	22,056	22,787
2013–2014	507	23,860	24,367
2014–2015	719	33,520	34,239
2015–2016	2,358	29,860	32,218
2016–2017	3,066	68,659	71,725
2017–2018	3,393	50,782	54,175
2018–2019	1,561	61,522	63,083
2019–2020	772	53,021	53,793
2020–2021	285	23,902	24,187
2021–2022	483	18,519	19,002
Total	**14,485**	**414,322**	**428,807**

Table 2 Number of new surgical trials (Datacut 5 November 2021, acknowledgement: NIHR CRN)

Qualification year (FY)	Commercial	Noncommercial	Total
2010–2011	3	28	31
2011–2012	3	29	32
2012–2013	8	40	48
2013–2014	16	42	58
2014–2015	13	84	97
2015–2016	16	79	95
2016–2017	17	107	124
2017–2018	37	130	167
2018–2019	18	139	157
2019–2020	12	106	118
2020–2021	18	95	113
2021–2022	13	59	72
Total	**174**	**938**	**1,112**

Figure 1 Portfolio composition and status (for financial year 2021–2022)





8,240
participants have been recruited

132
studies have recruited

There are now 25 SSLs (Table 3), nine chairs (Table 4) and nine surgical trials centres (Table 5). The SSLs lead their own trials, but the ethos of the SSL role is to develop new Chief Investigators across the NHS. The Chairs have expertise in both the design and delivery of trials. The trials centres are recognised for their expertise in surgical trial methodology and recruitment.

Table 3 RCS England SSLs

Current SSLs

SSL	Specialty	Location	Funder
Prof Peter Friend	Transplantation	Oxford	Rosetrees Trust
Mr Stuart McIntosh	Breast	Belfast	Breast Cancer Now & Association of Breast Surgery (ABS)
Ms Shelley Potter	Breast	Bristol	Breast Cancer Now & Association of Breast Surgery (ABS)
Prof Gavin Murphy	Cardiothoracic	Leicester	Society for Cardiothoracic Surgery (SCTS)
Mr Nigel Hall	Paediatric	Southampton	SPARKS/GOSH & British Association of Paediatric Surgeons (BAPS)
Prof Keith Roberts	Pancreatic cancer	Birmingham	Pancreatic Cancer Research Fund & Pancreatic Cancer UK
Prof Tim Underwood	Oesophageal cancer	Southampton	Association of Upper Gastrointestinal Surgery (AUGIS) & Heartburn Cancer UK
Mr Matt Gardiner	Plastic and hand surgery	Oxford	British Society for Surgery of the Hand (BSSH) & British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
Ms Emma Reay	Hand	Newcastle	British Society for Surgery of the Hand (BSSH)
Mr Robert Jones	Colorectal liver metastases	Liverpool	Bowel Cancer UK
Mr Douglas Hammond	Oral and maxillofacial surgery	Lancashire	British Association of Oral and Maxillofacial Surgeons (BAOMS) & Saving Faces
Prof Susan Moug	Colorectal surgery	Glasgow	Association of Coloproctology (ACPGBI) & Bowel Research UK
Mr Dale Vimalachandran	Colorectal surgery	Chester	Association of Coloproctology (ACPGBI) & Bowel Research UK
Prof Daniel Perry	Orthopaedic	Oxford	British Orthopaedic Association (BOA)
Prof Paul Baker	Orthopaedic	Newcastle	British Orthopaedic Association (BOA)
Prof Xavier Griffin	Trauma	Oxford	British Orthopaedic Association (BOA)
Prof Caroline Moore	Urology	London	British Association of Urological Surgeons (BAUS)
Prof Michael D Jenkinson	Neurosurgery	Liverpool	Society of British Neurological Surgeons (SBNS)
Mr Dimitrios Pournaras	Bariatric surgery	Bristol	British Obesity & Metabolic Surgery Society (BOMSS)
Mr George Smith	Vascular surgery	Hull/York	Vascular Society & Circulation Foundation
Prof Matt Bown	Vascular surgery	Leicester	Vascular Society & Circulation Foundation
Mr Dan Carradice	Vascular surgery	Hull/York	Vascular Society & Circulation Foundation
Ms Louise Wan	Gynaecological oncology	Manchester	British Gynaecological Cancer Society (BGCS)
Mr Filipe Correia Martins	Gynaecological oncology	Cambridge	British Gynaecological Cancer Society (BGCS)
Mr James O'Hara	ENT	Newcastle	ENT UK

Table 3 (continued) RCS England SSLs

Past SSLs

SSL	Specialty	Location	Funder
Prof Abhilash Jain	Plastic and hand surgery	London	British Society for Surgery of the Hand (BSSH) & British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)
Prof Jane Blazeby	Upper GI	Bristol	Association of Upper Gastrointestinal Surgery (AUGIS)
Prof Adele Francis	Breast	Birmingham	Breast Cancer Now & Association of Breast Surgery (ABS)
Prof Anne Schilder	ENT	London	ENT UK
Prof Matt Costa	Trauma	Oxford	Orthopaedic Research UK (ORUK)
Prof Amar Rangan	Orthopaedic	York	Orthopaedic Research UK (ORUK)
Mr Simon Bach	Colorectal	Birmingham	Association of Coloproctology (ACPGBI) & Bowel Research UK
Prof Ian Chetter	Vascular surgery	Hull	Vascular Society and Circulation Foundation
Mr Sam McClinton	Urology	Aberdeen	British Association of Urological Surgeons (BAUS)
Prof David Taggart	Cardiovascular	Oxford	George Drexler Foundation
Prof Dae Kim	Endocrine	London	British Association of Endocrine and Thyroid Surgeons
Prof Jim McCaul	Oral and maxillofacial surgery	London	British Association of Oral and Maxillofacial Surgeons (BAOMS) & Saving Faces

SSL = surgical specialty lead

Table 4 RCS England Chairs

Chair	Funder	Location
Prof David Jayne	Bowel Cancer UK	Leeds
Prof Joy Adamson	Mary Kinross	York
Prof Amar Rangan	Mary Kinross	York
Prof Michael Douek	Rosetrees Trust	Oxford
Prof David Beard	Rosetrees Trust	Oxford
Prof Tom Pinkney	George Drexler Foundation	Birmingham
Prof Cliona Kirwan	Masonic Charitable Foundation	Manchester
Prof Michael D Jenkinson	Sir John Fisher Foundation	Liverpool
Prof Rob Hinchliffe	Enid Linder	Bristol
Senior Lecturer: Natalie Blencowe	Enid Linder	Bristol

Table 5 RCS England Surgical Trials Centres

RCS England Surgical Trials Centre	Location	Directors
Birmingham Surgical Trials Consortium	Birmingham	Prof Dion Morton
		Prof Peter Brocklehurst
		Prof Pam Kearns
		Prof Tom Pinkney
		Dr Laura Magill
Bristol Surgical Trials Centre	Bristol	Prof Jane Blazeby
		Prof Rob Hinchliffe
Leeds Surgical Trial Centre	Leeds	Prof David Jayne
		Prof Julia Brown
		Prof Deborah Stocken
North West Surgical Trials Centre	Liverpool/Manchester	Prof Nigel Bundred
		Prof Paula Ghaneh
		Prof Cliona Kirwan
		Prof Michael Jenkinson
Surgical Intervention Trials Unit	Oxford	Prof David Beard
		Prof Michael Douek
		Prof Andy Carr
York Trials Unit	York	Prof David Torgerson
		Prof Amar Rangan
		Prof Joy Adamson
		Dr Catriona McDaid
National Facial Oral and Oculoplastic Research Centre	London	Prof Iain Hutchison
Aberdeen Surgical Trials Centre	Aberdeen	Prof Marion Campbell
		Prof Graeme MacLennan
		Prof James N'Dow
		Prof Craig Ramsay
Leicester Surgical Trials Centre	Leicester	Prof Gavin Murphy

Trainee engagement has been fundamental both at an individual level and in terms of the trainee research collaboratives (Figure 2). The SSLs work with Associate SSLs in developing and delivering research in their own specialties. The trainee research collaboratives have been instrumental in delivering both their own research studies and contributing to recruitment. Over 15,000 doctors and medical students from 155 countries have entered patients into collaborative studies, and over 70,000 patients have now been entered in collaborative audits, cohort studies or randomised trials, with over 100 publications citing collaborative research methodology. The trainee collaborative concept pioneered in surgery has also been developed by other specialties, including geriatric medicine, trauma, anaesthetics, gastroenterology, haematology, psychiatry and general practice. The same concept has also been developed by medical students.

The contribution of trainees to clinical trials is now being formally recognised by two mechanisms. Firstly, the collaborative authorship model so that contributors are appropriately indexed on PubMed, and secondly through the RCS England–NIHR Associate Principal Investigator (PI) (API) Scheme. The status of Associate PI is awarded to the trainee PI for each trial or study site.

Figure 2 Trainee research collaboratives

Focus on surgical specialties

The achievements of the RCS England Clinical Research Initiative are recognised not only in terms of academic output but also, more importantly, in terms of changing practice and impact. This section will present the key successes and major outputs of the various surgical specialties.

Upper gastrointestinal surgery

Upper gastrointestinal (UGI) surgery has had several trials funded and completed during the last decade. This expansion makes it internationally competitive and world leading in some subspecialties. The first UGI SSL (Professor Jane Blazeby) led the development of a portfolio of trials in oesophagogastric cancer and hepatopancreatico-biliary malignancies, as well as benign UGI disease and bariatric surgery. The trials are providing the highest evidence that will contribute to systematic reviews, meta-analyses and health policy and clinical decision-making. Studies nested in these trials have examined how to improve surgical trial conduct of general relevance to other fields. UGI was separated into four SSL posts after Professor Blazeby stepped down (oesophagogastric, liver, pancreas and bariatric surgery).

Some studies and nested methodological projects completed under Professor Blazeby's leadership are listed with references listed below:

Oesophageal cancer

In the 1990s and 2000s, UK surgeons led practice-changing trials (e.g. OEO2 and MAGIC) that defined the current treatment pathway for patients with oesophageal and gastric cancers. This history of world leading interdisciplinary research has been reinforced and expanded in the last 10 years with a focus on understanding the molecular basis of these cancers and improving outcomes after multimodal therapies. For example, surgeons have played leading roles in the following:

- A series of papers describing the genomic landscape of oesophageal cancer and highlighting therapeutic vulnerabilities for precision medicine.[2–8]
- The development and application of Enhanced Recovery after Oesophageal Surgery (ERAS), improving patient outcomes and reducing length of stay.[9,10]

- Pioneering prehabilitation before oesophagectomy to improve fitness for surgery and mitigate the effects of preoperative chemotherapy, leading to widespread NHS application.[11–14]
- Conducting a worldwide audit of techniques and outcomes for oesophagogastric anastomosis highlighting variation in surgical technique and management of anastomotic leak based on case volume and country income level.[15–17]
- The ROMIO trial, a blinded RCT comparing laparoscopically assisted versus open oesophagectomy for cancer (recruitment completed on time).[18]

Most recently, during the COVID-19 pandemic, surgical research has flexed rapidly to understand the burden of COVID-19 on surgical services for UGI cancers. Finally, surgical researchers have utilised the UK National OesophagoGastric Cancer Audit (NOGCA) dataset and machine-learning techniques to develop the most accurate prognosis prediction models in existence.[19,20] We have also developed a core information set and novel methods for embedding quality assurance for surgical interventions in trials.

Bariatric surgery

With the current obesity epidemic, bariatric surgery has been established as safe in the perioperative period and effective in the long term. The focus in the last decade has been on comparing different bariatric surgery modalities.

- The NIHR HTA By-Band-Sleeve Study has completed recruitment of 1,341 patients from 12 UK centres and is the world's largest trial in bariatric surgery. The By-Band-Sleeve Study is examining the clinical and cost effectiveness of gastric band, gastric bypass and sleeve gastrectomy.[21–23]
- By-Band-Sleeve developed a core outcome set for bariatric surgery.[24–26]
- Methods to cost bariatric interventions were developed in By-Band-Sleeve.[27–29]
- A By-Band-Sleeve substudy is the Metabolomics Study. The aim of this study is to assess the body's response to weight loss following bariatric surgery.

Gallbladder surgery

- The NIHR HTA C-Gall trial has completed recruitment. Patients are randomised to laparoscopic cholecystectomy or observation/conservative management for preventing recurrent symptoms and complications in adults with uncomplicated symptomatic gallstones. It has completed recruitment from over 20 UK centres.[1]
- The NIHR HTA Sunflower Study has opened in 50 UK centres and has randomised over 5,000 patients. It is examining the clinical and cost-effectiveness of imaging or expectant management in patients undergoing laparoscopic cholecystectomy at low or moderate risk of common bile duct stones.30 The study was the largest contributor to the API scheme apart from the COVID-19 RECOVERY study and has pioneered recruitment from the private sector.

Pancreatic surgery

For two decades, European Study Group for Pancreatic Cancer (ESPAC) studies have largely defined the evidence base for adjuvant chemotherapy in pancreatic cancer. However, many randomised trials, such as of Vandetanib (a tyroxine kinase inhibitor) in advanced cancer, and regimes of chemoradiotherapy for locally advanced unresectable cancer, have failed to demonstrate benefit.[2,31,32] Moves towards trial designs aimed at increasing recruitment through umbrella studies or having multiple arms aim to overcome problems with recruitment and a rigid design. One such ongoing study is the 'Precision Panc' platform, which seeks to determine genetic targets for therapy with early and late phase trials for resectable and unresectable cancer.[33]

It has been demonstrated that concomitant venous and pancreatic resection has outcomes equivalent to those undergoing pancreatic resection alone, effectively increasing the population of patients who can benefit from surgery.[34] The UK was an early adopter of centralised services for pancreatic surgery, with a consequent reduction in 90-day mortality compared with similar European countries without centralisation.[35] The UK has also led and reported a trial of two types of anastomoses in partial pancreatico-duodenectomy (the PANasta Trial).[36]

In addition to novel trial design, a focus on the patient pathway has been determined as a research priority.[37] Whereas positron emission tomography–computed tomography (PET-CT) aids in staging potentially resectable pancreatic cancers,[38] a rapid pathway to surgery can reduce the time to surgery, increase resection rates and reduce costs and harm.[39] Unwarranted variation in the diagnostic and treatment pathway is being explored in the RICOCHET national audit,[40] demonstrating varying compliance with national guidelines. Undertreatment of pancreatic exocrine insufficiency is important, as correction through the use of pancreatic enzyme replacement therapy improves survival among those with resectable or unresectable cancer where the treatment effect appears to be of similar magnitude to that of surgery or chemotherapy.[41]

The next decade will see trials of neoadjuvant therapy, standardisation of patient care and a much greater emphasis upon patient experience and reported outcomes.

Major findings:

- Gemcitabine established as an effective and widely tolerated adjuvant therapy;
- the addition of capecitabine to Gemcitabine confers additional survival benefit after resectional surgery;
- reduction in 90-day mortality across the UK following centralisation of surgical services and increasing centre volume contrasts with countries without centralisation;
- unwarranted variation in diagnostic and treatment pathways provide opportunities to standardise and improve care;
- enzyme replacement therapy is an effective therapy in pancreatic cancer and yet is underused;
- the Cancer Research UK (CRUK) funded PANasta trial compared two types of duct-to-mucosa pancreatic anastomosis in patients with pancreatic cancer.

Colorectal surgery

Colorectal surgery in the UK has changed dramatically over the last 10 years to become an international success story. Early collaboration was evident in 2013 with research sandpit events and The Delphi Priority Exercise—an initiative led by ACPGBI (Association of Coloproctology of Great Britain and Ireland) and supported by the BDRF (Bowel Disease Research Foundation) that surveyed ACPGBI members to develop 25 research questions.[42] ORACLE (BOwel Research PAtient ConsuLtation Exercise) then took these questions to the patients and public to ensure they were relevant and needed by patients.[43] These strategies have led to a number of large-scale NIHR funded trials that are in progress (PREPARE-ABC; CIPHER) or completed (ROCSS)[44]; national and international collaborations (STAR-TREC, in progress) and high-impact publications all with a focus on involving patients (International consensus definition of low anterior resection syndrome, completed).[45] International collaborative efforts continue at pace in 2020 with the development of new global research questions (FALCON, EAGLE, Damascus, The Plato Project; all underway).

More recent studies have focused on some of the more common, but less investigated, questions such as wound infection (SUNRRISE, completed). These studies have also adopted efficient trial designs, such as the ROSSINI2 study (in progress, led by first Colorectal SSL Mr Simon Bach), which uses a multi-arm multi-stage (MAMS) design to investigate methods to reduce wound infection after surgery.

It has also been essential that new researchers (consultants, trainees, medical students and patients) continue to be introduced to research to ensure this work continues with trainees now leading their own research with the support of the trainee collaboratives, Surgical Trials Centres and MRC Trials Hubs for Trials Methodology. This has been done through SSL initiatives such as Granule (Generating Surgical Recruiters for Randomised Trials; https://www.acpgbi.org.uk/professionals/research_audit/acpgbi/granule.aspx and CREATE Roadshows (Colorectal Research and Trial Engagement; https://www.acpgbi.org.uk/events/659/create_colorectal_research_and_trials_engagement_roadshow) that have travelled around the country promoting current colorectal trials that encourage engagement and allow everyone in our specialty to believe they can contribute, collaborate and even lead the next generation of colorectal research. The trainee collaboratives continue to impress with recent high impact publications and the attraction of mainstream media. All of this is supported by a supportive and collaborative social media presence: the future looks bright for #colorectalresearch.

Colorectal liver metastases and hepatobiliary cancer

The UK is the world leader in designing and delivering surgical trials in colorectal liver metastases and hepatobiliary malignancies. The development of regional cancer networks and referral pathways to tertiary hepatobiliary surgical centres make the UK ideally equipped to deliver studies in what are often small groups in a very heterogeneous population.

UK surgically led studies have defined standard of care in the use of perioperative chemotherapy for colorectal liver metastases, as well as adjuvant therapy for resected biliary tract cancers.[46,47] The UK is also a major contributor to the ORANGE trials comparing laparoscopic with open liver resection. The UK has also attempted ambitious randomised studies comparing surgery with systemic chemotherapy for resectable colorectal lung metastases, as well ablation with resection for colorectal liver metastases.[48,49] All have failed to recruit and have been closed prematurely. Suggested reasons for these failures include lack of clinician equipoise, lack of patient equipoise and the heterogeneity of patient populations. A new approach is therefore essential to develop high level evidence to guide patient and clinician decision making around metastatic rectal cancer. The ACCELERATOR (AdvanCed ColorEctaL CancER PlATfORm) Study is a novel prospective cohort platform study that will capture meaningful patient-reported outcomes for patients with metastatic colorectal cancer. This study will be entirely online and will link with national colorectal cancer datasets (MRC CORECT-R) to provide high-fidelity clinically meaningful data around this complex patient group. The study will allow patient self-registration via an online portal, widening access to all patients, not just those treated in research-active centres.

Breast surgery

Breast cancer research in the UK is a multidisciplinary undertaking, in which breast surgeons have traditionally been very active and have often assumed leadership roles in key clinical trials. Over the last decade there has been significant clinical research activity contributing to improvements in our understanding of breast cancer biology and breast cancer treatment. To support this activity, in 2013 the Association of Breast Surgery (ABS) established an Academic and Research Committee (ARC) to promote surgical research and innovation. The ABS ARC is also a grant-awarding body, awarding pump-priming grants for breast surgical research, including an annual New Investigator award to support new researchers. Key achievements and ongoing work are outlined below.

Completed projects:

- iBRA—this trainee collaborative led project rapidly recruited over 2,000 patients to a prospective cohort of women undergoing immediate postmastectomy implant-based reconstruction.[50]
- The subsequent iBRA2 study was delivered through a similar collaborative model and looked at the impact of reconstruction surgery on delays to adjuvant therapy.[51]
- The TEAM study evaluated the safety and efficacy of therapeutic mammoplasty as an alternative to mastectomy for breast cancer.[52]
- The NIHR HTA-funded POSNOC trial is the largest UK-led international breast cancer surgical trial. It has successfully recruited 1,900 patients across the UK, Australia and New Zealand, and is comparing surgery (or radiotherapy) with no further axillary treatment in early breast cancer patients with a positive sentinel lymph node. This trial is currently in follow-up and results are awaited.
- The completion and publication of a breast surgical research gap analysis, which has identified key research gaps in breast surgery.[53]
- UK multicentre prospective audit of breast cancer management pathways during the Covid-19 pandemic, tracking the treatment of more than 3,000 patients with early breast cancer during early-mid 2020.[54]
- More than 1,000 patients recruited to the collaborative-delivered NeST study (a prospective study of neoadjuvant systemic therapy in breast cancer). Initial results have been published, and the main study paper is currently under review following revision at *British Journal of Surgery*.[55]
- Publication of an overview of innovations for the future of breast surgery, in response to the RCS England Commission for the Future of Surgery workstream.[56]

In progress:

- Successful NIHR HTA funding for three innovative, surgically led breast cancer trials in the UK.
  - SMALL: a phase III RCT comparing surgery with minimally invasive vacuum assisted excision of small screen-detected breast cancer (https://fundingawards.nihr.ac.uk/award/17/42/32).[57] Currently open with >100 patients recruited, despite extensive set-up and recruitment challenges associated with the pandemic.
  - ATNEC: a phase III RCT assessing de-escalation of axillary surgery after neoadjuvant chemotherapy in early breast cancer (https://fundingawards.nihr.ac.uk/award/NIHR128311). Currently in set-up.
  - EndoNET: a phase III RCT comparing neoadjuvant endocrine therapy with standard surgical treatment for postmenopausal women with oestrogen receptor (ER)-positive breast cancer. Currently in set-up.
- Successful NIHR HTA funding for a further neoadjuvant study in human epidermal growth factor receptor 2 (HER2)-positive breast cancer with joint surgical leadership (https://fundingawards.nihr.ac.uk/award/NIHR131362)
- The establishment of a breast reconstruction network (iBRA-NET, https://www.ibra-net.com/) for future studies in breast surgery, including oncoplastic and reconstructive surgery and other studies of devices and technologies. The network has a number of projects either underway or in set-up: these include the Pre-BRA, Best-BRA and Map-BRA studies looking at implant reconstruction,the MARECA study (a prospective multicentre cohort study to examine the management of locoregional breast cancer recurrence), the impalpable lesion localisation study and the ANTHEM study, evaluating patient-reported outcomes from oncoplastic breast surgery and mastectomy with or without reconstruction.[58–61]
- Ongoing Association of Breast Surgery James Lind Alliance Research Priority Setting Partnership, which will be completed in early 2022 and announced at the ABS Conference in May 2022, and will be published thereafter.

Urology

Prostate cancer research in the UK has had strong surgical representation over the last three decades. These have ranged from the CAP screening study to PROTECT, randomising men with localised prostate cancer between active monitoring, radical prostatectomy and radical radiotherapy.[62, 63] The combining of the previous prostate cancer charities Prostate Action and the Prostate Cancer Charity into the single Prostate Cancer UK in 2012, when ‘Movember’ was looking for a single men’s health partner in the UK, represented a step change in approach. Prostate cancer research in the UK, where surgeons are both partners and leaders, has changed international practice, from prostate magnetic resonance imaging studies led by surgeons to treatment studies in metastatic disease with surgical collaborators.

The Urology trainee collaborative, British Urological Researchers in Surgical Training, officially launched by Veeru Kasivisvanathan in 2015, has followed the model of the general surgical trainees’ research collaborative.[64] Their first international collaborative project, MIMIC, recruited over 4,000 patients from 71 sites in seven countries in 4 months.[65] It showed that white cell count is not associated with spontaneous passage of ureteric stones. The data have been used to create a stone passage risk calculator, to help direct earlier surgical treatment when needed. By late 2021, BURST had three completed studies, two ongoing and two upcoming.

In 2019, The Urology Foundation (TUF), which is committed to working across all urological diseases, set up the Urology Trials Unit (UTU)—a joint effort with the British Association of Urological Surgeons (BAUS) and RCS England, with the BAUS President Tim O’Brien and the RCS England Urology SSL Caroline Moore working with TUF to set up the UTU. A competitive process led to the appointment of the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen, led by Professor Graeme MacLennan, medical statistician, and Professor James N’Dow, consultant urologist.

A Dragon’s Den approach at the 2021 BAUS Annual meeting identified the first two UTU dedicated projects, taking forward ideas from new investigators for development for funding and implementation.

Vascular surgery

Vascular surgery has benefitted from a strong evidence base for traditional surgical practice, supported largely by landmark RCTs such as the UK Small Aneurysm Trial and the European Carotid Surgery Trial.[66,67] The Circulation Foundation has made a particularly noteworthy contribution to vascular research in the UK, largely via its funding for

upcoming researchers at critical career points. These researchers have gone on to secure significant future funding from large national funding bodies.

Vascular surgery became an independent speciality in 2012. Since that time vascular surgery has become increasingly multidisciplinary, with patients benefiting from a growing focus on vascular and preventative medicine, perioperative care and endovascular/percutaneous interventions. The strong vascular surgical research environment now reflects this breadth of expertise. This is supported by an active and world leading trainee research collaborative, the Vascular and Endovascular Research Network, who delivered the international COVER study of outcomes for vascular patients during the COVID-19 pandemic.[68] Data from COVER are now informing research applications into new approaches to the care of vascular patients. The development of a series of core outcome sets (COS) for vascular disease has been initiated, with COS for amputation completed and COS for aortic aneurysm and diabetic foot ulceration in progress. Together with a recent public priority setting exercise recently completed by the Vascular Society of Great Britain and James Lind Alliance, there is a strong basis for future research applications that will benefit patients with vascular disease and answer the questions of greatest importance to patients themselves.

Completed research 2011–2020 (key studies with funding >£0.5 million):

- EVRA: NIHR HTA, £1.8 million. A randomised clinical trial to compare early versus delayed treatment of superficial venous reflux in patients with chronic venous ulceration (RCT).[69]
- IMPROVE: NIHR HTA, £1.4 million. Can emergency endovascular aneurysm repair (eEVAR) improve the survival from ruptured abdominal aortic aneurysm? (RCT).[70]
- AAA GWAS: Wellcome Trust, £0.6 million. Genome-wide association study (GWAS) of abdominal aortic aneurysm (AAA) (fundamental research).[71]
- ACST2: NIHR HTA, £1.4 million. Asymptomatic Carotid Surgery Trial-2 (ACST-2): an international randomised trial to compare carotid endarterectomy with carotid artery stenting to prevent stroke (RCT).[72]
- AARDVARK: NIHR HTA, £0.9 million. An evaluation of the effect of an angiotensin-converting enzyme inhibitor on the growth rate of small abdominal aortic aneurysm (RCT).[73]
- CLASS: NIHR HTA, £1.1 million. RCT comparing foam sclerotherapy, alone or in combination with endovenous laser therapy, with conventional surgery as a treatment for varicose veins.[74]
- VenUS IV: NIHR HTA. RCT of compression hosiery versus compression bandaging in the treatment of venous leg ulcers.[75]
- SWSHI: NIHR Programme Grants for Applied Research (PGfAR), £2.0 million. Surgical wounds healing by secondary intention: characterising and quantifying the problem and identifying effective treatments (programme grant with pilot RCT).[76]

Research in progress:

- BASIL 3: NIHR HTA, £1.9 million, ended 2021. A multicentre trial comparing traditional peripheral angioplasty with or without stenting with treatment with drug eluting technology (RCT).
- NESIC: NIHR EME, £1.1 million, ended 2021. Does neuromuscular electrical stimulation improve the absolute walking distance in patients with intermittent claudication compared with best available treatment? (RCT).
- MIDFUT: NIHR HTA, £1.8 million, ended 2022. Multiple Interventions for Diabetic Foot Ulcer Treatment (MIDFUT) Trial (RCT).
- SWSHI2: NIHR HTA, £1.6 million, ended 2022. A pragmatic multicentre RCT to assess the clinical and cost effectiveness of negative pressure wound therapy versus usual care for surgical wounds healing by secondary intention.
- BASIL 2: NIHR HTA, £2.0 million, ends 2023. A multicentre trial comparing open surgical bypass with peripheral angioplasty with and without stenting (RCT).
- NIHR HTA, £1.4 million, ends 2023. Diagnostic tools to establish the presence and severity of peripheral arterial disease in people with diabetes (Medical technology assessment).
- UKAGS: British Heart Foundation (BHF), £1.5 million, ends 2023. UK Aneurysm Growth Study (Fundamental research).
- CHAPS: NIHR HTA, £0.9 million, ends 2023. Compression hosiery to avoid postthrombotic syndrome (RCT).
- Hook and loop compression: NIHR HTA, £1.9 million, ends 2024. A RCT of compression therapies for the treatment of venous leg ulcers.

- UK-COMPASS: NIHR HTA, £1.1 million, ends 2024. A risk-adjusted and anatomically stratified cohort comparison study of open surgery, endovascular techniques and medical management for juxtarenal aortic aneurysms: the UK COMplex AneurySm Study (Registry).
- CRISP: NIHR advanced fellowship, £0.9 million, ends 2024. Cardiovascular risk reduction In the NHS AAA screening programme: a codeveloped cardiovascular prevention intervention (RCT).
- SOLEFUL: NIHR doctoral research fellowship (DRF), £0.5 million, ends 2024. Evaluating shockwave therapy of lower extremity diabetic foot ulcers (feasibility study).
- Targeted AAA screening: NIHR Health and Social Care Delivery Research (HSDR), £0.6 million, ends 2024. In silico trials of targeted screening for abdominal aortic aneurysm using linked healthcare data (data science).
- Three-dimensional (3D) ultrasound: NIHR Career Development Fellowship, £0.6 million, ends 2024, Developing tomographic 3D ultrasound for cardiovascular screening (medical technology assessment).
- Personalised AAA management: MRC Future Leaders Fellowship, £1.5m, ends 2025, Defining personalised management strategies for people with AAA (fundamental research).
- PHAST: NIHR PGfAR, £2.4m, ends 2029, Peripheral arterial disease, High blood pressure and Aneurysm Screening Trial (programme including RCT).

Paediatric surgery

Paediatric surgery in the UK has had a slow but steady trickle of RCTs over the past 20 years, led primarily from a single centre. There was also a fledgling trainee collaborative research. The formation of the SSL post in early 2018 has facilitated the advancement of RCTs and, whereas the wider program is still in its infancy, significant gains have been made. Over the past 2 years, there has been significant interest among UK paediatric surgeons in developing and participating in RCTs. A clinical studies group has been developed specifically for this purpose, comprising consultants, researchers and trainees. Through this, several trials have already been completed, several have successfully achieved funding and are in progress and a number more are in the planning stage, seeking competitive funding. The specialty is moving away from a fragmented single-centre approach to research, towards a more collaborative cohesive network and developing a more evidence-based approach.

In 2019, a wide group of children's surgeons from specialist and general centres contributed to a project to identify research priorities in the field of general surgery of childhood. This has led to the development of 20 priority research questions that have been distributed to national funding bodies and we hope will be a target for researchers to address in the years to come.[77] Development of the trainee research collaborative has also been supported; the collaborative has completed several observational studies with others in progress and further in development.[78]

It is clear that the benefit of the program in paediatric surgery is truly beginning to materialise. This is measurable not only in the number of studies that have achieved funding or been submitted for funding but also in the number of individuals now involved in the research process, and as principal or chief investigators (CI), as well as trainees via the API scheme.

Completed studies:

- CONservative TReatment of Appendicitis in Children—RCT (Feasibility)—CONTRACT(F). NIHR HTA funded. CI N Hall, three new PIs (H Corbett (Alder Hey), M Stanton (Southampton), D Rex (St Georges)). Completed Autumn 2018.[79–83]
- Children with AppendicitiS during the CoronAvirus panDEmic (CASCADE)—multicentre observational cohort study of management and outcomes of children during COVID-19 pandemic; 80 UK centres involved, completed October 2021.[84]

Studies in progress:

- Children's Surgical Outcome Reporting (C-SOR) NIHR HSDR funded. CI M Knight, S Kenny (new CI), new PIs N Lansdale (Manchester), A Long (Cambridge) and T Bradnock (Glasgow). Started Autumn 2019.
- Timing of Stoma Closure in Neonates (ToSCiN). NIHR HTA funded. New CI, N Lansdale (Manchester) with dedicated formal mentoring support as part of the grant for N Hall, five new PIs appointed and use API scheme. Started Spring 2020.[85]

- Treatment of Oesophageal Atresia STrictures (TOAST). NIHR HTA funded. CI N Hall, new co-CI I Yardley (Evelina London), will engage 10–15 new PIs and use API scheme. Formal mentoring in grant for I Yardley by N Hall. Started Spring 2021.
- CONservative TReatment of Appendicitis in Children (RCT) CONTRACT 2. NIHR HTA funded. CI N Hall, multiple new PIs, using API scheme. Started June 2021.
- International Congenital Lung Malformation Registry (ICLMR)—global registry; new CI M Stanton (Southampton). Funded by Newlife charity, started Summer 2020. Will engage multiple new PIs from UK and overseas.
- CHAPS—Clinical and Histological Assessment of Predictors of Disease Severity in Balanitis Xerotica Obliterans (Lichen Sclerosus et atrophicus of the male genitalia): a prospective observational study. Funded by the Urology Foundation, new CI H Corbett (Alder Hey). Started February 2022.

Elective orthopaedic surgery

Over the last decade there has been an expansion in the number of adult elective orthopaedic surgery trials. The successful completion of the trials in elective orthopaedics listed below combined with the impact of a number of successful trauma and paediatric orthopaedic trials that have changed national practice/National Institute for Health and Care Excellence (NICE) guidance have encouraged the orthopaedic research workforce and led to an increase in research activity in elective orthopaedics. The research infrastructure with orthopaedics has been supported not only by the RCS England but also by the British Orthopaedic Association (BOA) who have invested in the development of specialist BOA-endorsed CTUs for orthopaedic trials. These included the appointment of York Trials Unit as the BOA Surgical Research Centre (BOSRC). This investment in capacity building gave orthopaedic surgeons access to methodological advice and collaboration, leading to the development of NIHR trials such as PROFHER2, UKFROST, OPAL, SOFFT and ACTIVE, including support and mentorship of several first-time CIs and co-investigators. More recent BOA-endorsed appointments in Nottingham and Exeter CTUs will expand the research infrastructure in the orthopaedic research community still further.

Currently there are over 20 active trials being delivered across a variety of orthopaedic subspecialties, including arthroplasty, knee surgery, shoulder surgery, spinal surgery and foot and ankle. The BOA has also supported changes to the training curriculum that have recognised the value and importance of research participation. This has empowered trainee researchers to get involved with research and has led to the development of a network of trainee orthopaedic research collaboratives. These networks have been instrumental in developing a pipeline of orthopaedic researchers and a research-ready workforce that have already supported the delivery of a number of orthopaedic trials through the API scheme, most notably through the WHITE3:Hemi trial.

Key NIHR-funded randomised trials and grants completed 2012–2022:

- KAT (Knee Arthroplasty Trial);[86]
- UKUFF (The United Kingdom Rotator Cuff Surgery Study);[87]
- APEX Study (Arthroplasty Pain Experience Study (APEX): RCT to determine whether local wound infiltration reduces chronic pain after lower limb arthroplasty);[88]
- TOPKAT (Total Or Partial Knee Arthroplasty Trial);[89]
- STAR Trial (The STAR trial: evaluation of a care pathway for patients with long-term pain after knee replacement);[90]
- SPAARK (Study of Peri-Articular Anaesthetic for Replacement of the Knee. The clinical and cost effectiveness of periarticular liposomal bupivacaine compared with bupivacaine hydrochloride for postoperative recovery after knee replacement surgery: a multi-centre, blinded, RCT);[91]
- REACTS (Return to employment after carpal tunnel release surgery: a prospective observational cohort study with a nested qualitative interview study);[92]
- START:REACTS (Subacromial spacer for Tears Affecting Rotator cuff Tendons: a Randomised, Efficient, Adaptive Clinical Trial in Surgery);[93]
- PEP-TALK (A behaviour change physiotherapy intervention to increase physical activity following hip and knee replacement: a pragmatic phase III RCT);[94]
- UKFROST (The United Kingdom Frozen Shoulder Trial);[95]
- OPAL (Occupational advice for Patients undergoing Arthroplasty of the Lower limb).[96]

Key NIHR research in progress:

- RACER-HIP (Robotic Arthroplasty: a Clinical and cost Effectiveness RCT for Hips);
- The ACL SNNAP Trial (ACL Surgery Necessity in Non Acute Patients. Comparison of the clinical and cost effectiveness of two management strategies for nonacute anterior cruciate ligament (ACL) injury);
- SISMIC Study: RCT of Scaffold InSertion and MIcrofracture Compared with Microfracture Alone for the Treatment of Chondral or Osteochondral Defects of the Knee;
- KARDS (Knee ARthroplasty versus joint Distraction Study for osteoarthritis);
- RACER-KNEE (Robotic Arthroplasty: a Clinical and cost Effectiveness RCT for knees);
- Partial Rotator Cuff Tear Repair Trial (PRoCuRe) (The clinical and cost effectiveness of surgical repair of partial rotator cuff tears in patients with subacromial shoulder pain: A comparison of surgical repair versus surgery with no repair);
- MAPPS: Mouth cAre to Prevent Pneumonia in older people Study;
- DIDACT (DIsplaced DistAl Clavicle Trial) Surgery compared with sling immobilisation in the management of adults with a displaced unstable fracture of the distal clavicle: a multicentre, non-inferiority, RCT;
- PERISCOPE: PERI-operative biologic DMARD management: Stoppage or COntinuation during orthoPaEdic operations;
- SarcoSIGHT: an RCT of fluorescence guided sarcoma surgery versus standard of care.

Children's orthopaedic surgery

Children's orthopaedic surgery in the UK is now recognised as the leader in multicentre clinical studies internationally, despite the relative infancy of the group. We recently published the nationwide British Orthopaedic Surgery Surveillance (BOSS) study, with a comprehensive cohort that ran at 143 hospitals investigating Perthes' disease and slipped epiphysis.[97,98] The success of the BOSS study created a wave of research interest from both surgeons, and funders. This has culminated in the group having a formal James Lind Alliance research agenda developed with surgeon and patient input,and an international trials portfolio worth over £35 million.[99] In part, the success of the group has been through their desire to innovate in the way that trials are delivered, with 'explainer animations' replacing traditional leaflets, text messages replacing traditional mail for follow-up and wholly online delivery of all elements of the study from set-up to close-down.

NIHR studies completed

- BOSS Slipped Epiphysis—a nationwide comprehensive multicentre cohort to identify the incidence, case mix, surgical intervention variables and outcomes (IDEAL 2b) of Slipped Capital Femoral Epiphysis. Published in the *Bone & Joint Journal*;[98]
- BOSS Perthes Disease—a nationwide comprehensive multicentre cohort to identify the incidence, case mix, surgical intervention variables and outcomes (IDEAL 2b) of Perthes Disease of the hip. Published in the *Bone & Joint Journal*;[97]
- FORCE—Forearm Fracture Recovery Evaluation—https://www.FORCEStudy.org. Published in the *Lancet*.[100]

NIHR HTA studies ongoing

- SCIENCE—Surgery or Casts for Injuries of the Epicondyle in Children. RCT. https://www.SCIENCEStudy.org (Recruiting throughout the UK, New Zealand and Australia);
- OSTRICH—Orthotics for Treatment of Symptomatic Flat Feet in Children. RCT;
- CRAFFT—Children's Radius Acute Fracture Fixation Trial. RCT. https://www.CRAFFTStudy.org;
- BASIS—Full-time bracing vs night-time only bracing for idiopathic scoliosis. RCT. https://www.BASISstudy.org;
- BigBOSS (in setup)—Open reduction vs pinning-in-situ for severe stable SCFE. RCT;
- ODDSocks (in setup)—Outcomes Displaced Distal Tibia Fractures: Surgery or Casts in Kids. RCT;
- PICBone (in setup)—Producing a decision tool for the diagnosis of musculoskeletal infection in children.

International trials

- The UK SCIENCE and CRAFFT Trials have recently been funded in the US (NIH R01), and are called the COMET and DRIFT studies, respectively. Their outcomes have been aligned with the UK studies to facilitate an end of study meta-analysis of individual patient data with the UK data.

NIHR fellowships

There are four personal NIHR fellowships related to children's orthopaedics:

- Adam Galloway (Leeds). Outcomes of physiotherapy in Perthes' Disease. NIHR DRF;
- Abhi Singh (Oxford). Machine Vision in the diagnosis of Developmental Hip Dysplasia. NIHR DRF;
- Daniel Perry (Liverpool). NIHR Clinician Scientist;
- Daniel Perry (Liverpool). Optimising trial design in hip dysplasia screening. NIHR Research Professorship.

Orthopaedic trauma surgery

Trauma is the leading cause of death in the young population and can result in devastating complications for the patients, their families and society thereafter. The associated direct and indirect costs secondary to trauma are vast and therefore investment from every healthcare system in prevention, improving outcomes and reducing costs, is of paramount importance. It is therefore no surprise that the number of trauma surgery trials has increased exponentially in the last few years, and this is projected to further increase. In fact, almost £12 million has already been invested in completed trials and another £28 million on ongoing trials.

Recently completed NIHR-funded randomised trials and grants:

- A feasibility study to compare contemporary uncemented hemiarthroplasty with the standard-of-care cemented hemiarthroplasty for the treatment of displaced intracapsular hip fractures. Cemented hemiarthroplasty resulted in a modestly but significantly better quality of life and a lower risk of periprosthetic fracture than uncemented hemiarthroplasty (award: £218,423.00);[101]
- World Hip Trauma Evaluation—WHITE 5: RCT to compare contemporary uncemented hemiarthroplasty with the standard-of-care cemented hemiarthroplasty for the treatment of displaced intracapsular hip fractures. Cemented hemiarthroplasty resulted in a modestly but significantly better quality of life and a lower risk of periprosthetic fracture than uncemented hemiarthroplasty (award: £349,832.00);[101]
- Moulded cast compared with K-wire fixation after manipulation of an acute dorsally displaced distal radius fracture: the DRAFFT 2 RCT. No difference in patient wrist function between K-wire fixation and moulded cast; however, 13% treated with moulded cast required further surgery within 6 weeks (award: £1,248,592.50);[102]
- Surgery versus conservative management of stable thoracolumbar fracture: the PRESTO feasibility RCT. A definitive trial is unlikely to be feasible currently (award: £338,089.00);[103]
- Negative-pressure wound therapy compared with standard dressings following surgical treatment of major trauma to the lower limb: the WHiST RCT. No evidence of a difference between incisional negative-pressure wound therapy and standard dressings in the rate of deep surgical site infection at 30 days (award: £1,655,969.00);[104]
- Retrograde intramedullary nail fixation compared with fixed-angle plate fixation for fracture of the distal femur: the TrAFFix feasibility RCT. This feasibility study had a lower than expected recruitment rate, identified the surgeon-related factors contributing to that, and proposed a modified protocol for a full trial (award: £235,841.63);[105]
- Treatment of first-time traumatic anterior shoulder dislocation: the UK TASH-D cohort study. Few NHS patients had surgery after their first shoulder dislocation, and further research would be needed to determine whether surgery prevents further dislocations (award: £348,217.84);[106]
- Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT. No evidence that negative pressure wound therapy improves outcomes after 12 months for adults with open fracture of the lower limb (award: £2,047,962.49);[107]
- Intramedullary nail fixation versus locking plate fixation for adults with a fracture of the distal tibia: the UK FixDT RCT. Both nail fixation and locking plate fixation had similar disability ratings at 6 months, but nail fixation costs less in the first year after the fracture (award: £1,297,692.00);[108]
- The Ankle Injury Management (AIM) trial. Closed chest compression provides a clinically equivalent outcome to operative rib fixation (ORIF) at reduced cost to the NHS and to society at 6 months (award: £1,979,554.74);[109]
- The ProFHER (PROximal Fracture of the Humerus: Evaluation by Randomisation) trial. A pragmatic multicentre RCT evaluating the clinical effectiveness and cost-effectiveness of surgical compared with nonsurgical treatment for proximal fracture of the humerus in adults. Surgical practice does not result in a better outcome for most patients with displaced fractures of the proximal humerus involving the surgical neck and is not cost-effective in the UK setting (award: £148,447.19);[110]
- UK DRAFFT. RCT of Percutaneous Fixation with Kirschner Wires versus Volar Locking-Plate Fixation in the Treatment of Adult Patients with a Dorsally Displaced Fracture of the Distal Radius. No difference between

Kirschner wires and volar locking plates for patients with dorsally displaced fractures of the distal radius (award: £1,300,498.87);[111]
- Treatment of severe ankle sprain: a pragmatic RCT comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial: the choice of treatment for severe ankle sprain may affect the speed of recovery but not the long-term outcome and that the decision about which brace to apply should incorporate an assessment of likely compliance and acceptability to patients (award: £388,142.00);[112]
- Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty. Support for use of total hip replacement in the management of displaced subcapital fracture of the hip in fit, older patients; arthroplasty was more clinically effective and probably less costly over a 2-year period postsurgery (award: £426,194.00);[113]
- L1FE: Lateral Compression Type-1 Fracture Fixation in the Elderly, RCT (award ID: 16/167/57) (award: £2,000,330.79).

Key NIHR research in progress:
- Scaphoid Waist Internal Fixation for Fractures Trial (SWIFFT) Cast treatment versus surgical fixation of fractures of the Scaphoid waist in adults: a multicentre RCT (award ID: 11/36/37) (award: £2,284,684.00);[114]
- WHIST—Wound Healing In Surgery for Trauma (Award ID: 14/199/14) (award: £1,655,969.00);[115]
- In younger adults with unstable ankle fractures treated with close contact casting, is ankle function not worse than those treated with surgical intervention? The FAME Trial (award ID: NIHR127273) (award: £1,477,519.58);
- Repair of digital nerve injury (award ID: NIHR127807) (award: £1,213,073.36);
- ERASER TRIAL: Early Rib Analgesia with Serratus. A pragmatic randomised control trial evaluating the clinical and cost-effectiveness of serratus anterior plane block with catheter insertion compared with usual care in patients with multiple rib fractures (award ID: NIHR130632) (award: £1,782,916.15);
- World Hip Trauma Evaluation—FRUITI: Fix or Replace Undisplaced Intracapsular fractures Trial of Interventions (award ID: NIHR128399) (award: £1,977,272.04);
- The ORIF Procedure mEchanisms of Rib fixAtion (OPERA) STUDY (award ID: NIHR132240) (award: £462,283.57);
- Evaluation of chest wall stabilisation through ORIF (ORIF Study) (award ID: 16/61/10) (award: £1,570,875.38);
- Suture fixation versus tension band wiring for simple olecranon fracture fixation: a multicentre RCT (Simple Olecranon Fracture Fixation Trial (SOFFT)) (award ID: NIHR127739) (award: £1,737,362.39);
- Acute Rehabilitation following Traumatic anterior shoulder dISlocAtioN (ARTISAN). A Multicentre RCT (award ID: 16/167/56) (award: £1,342,464.98);
- External frame versus internal locking plate for articular pilon fracture fixation: a multicentre RCT (award ID: 15/130/84) (award: £1,986,053.00);
- PROFHER-2: Effectiveness and cost-effectiveness of reverse shoulder arthroplasty versus hemiarthroplasty versus nonsurgical care for acute 3 and 4 part fractures of the proximal humerus in older adults. The PROFHER-2 Randomised Clinical Trial (award ID: 16/73/03) (award: £2,697,273.62);
- The HUmeral SHaft fracture trial (HUSH) (award ID: NIHR127817) (award: £1,138,386.93);
- POINT: A multicentre randomised trial of surgery versus nonsurgical splint treatment for proximal phalanx shaft finger fractures in adults (award ID: NIHR127292) (award: £1,224,944.02);
- DENS RCT: Duration of External Neck Stabilisation following odontoid fracture in older or frail adults: a RCT of collar versus no collar (award ID: NIHR131118) (award: £1,922,133.60);
- Prospective RCT comparing three splints for finger flexor tendon repairs (FIRST study) (award ID: NIHR133582) (award: £1,151,006.71);
- DUALITY: Dual mobility (DM) versus standard articulation total hip replacement (THR) in the treatment of older adults with a hip fracture (award ID: NIHR203115) (award: £349,080.00);
- The Hemi SPAIRE study: The effects of a modified muscle sparing posterior technique (SPAIRE) in hip hemiarthoplasty for displaced intracapsular fractures on postoperative function compared with a standard lateral approach; RCT (award ID: PB-PG-0817-20039) (award: £450,509.00).

Plastic surgery and hand surgery

Both plastic surgery and hand surgery have historically had low levels of RCT activity. In 2013, the Reconstructive Surgery Trials Network (RSTN) was created by Abhilash Jain (first plastic surgery SSL) and Matthew Gardiner (Trainee Lead). It has boosted collaborative working in the specialties and with interface specialties, such as breast surgery[50], dermatology, trauma and orthopaedics, and anaesthesia. The RSTN has established a systematic review group to support trial ideas and is developing online learning resources. The RSTN has supported the setting up of similar networks in the Netherlands and Australia and continues to build international links.

The roles are supported by the British Association for Plastic, Reconstructive and Aesthetic Surgery and the British Society for Surgery of the Hand (BSSH). The BSSH has subsequently funded an additional Hand Surgery SSL (Emma Reay) to further develop the involvement of hand surgeons across both specialties in clinical trials. The BSSH has integrated the SSL roles into their committee structure, inviting both to be members of the research committee to further promote, integrate and facilitate surgical trials in hand surgery.

Completed NIHR studies

- The NIHR HTA-funded DRAFFT trial found that there was no difference between Kirschner wire fixation and volar locking plate fixation for patients with dorsally displaced distal radial fractures.[116]
- The NIHR HTA-funded SWIFFT trial found that cast immobilisation was not inferior to fracture fixation for minimally displaced scaphoid fractures, which has informed nationwide changes to scaphoid fracture management.[117]
- The NIHR RfPB-funded NINJA Trial investigated replacing or discarding the nail plate following nail bed repair and will report imminently.[118]

Ongoing NIHR studies

- The NIHR HTA-funded DISC trial aims to compare Collagenase with surgical intervention for the management of patients with Dupuytren's disease.
- An NIHR-funded Hand 2 trial of percutaneous needle fasciotomy versus limited fasciectomy is currently underway.
- The NIHR HTA-funded POINT trial investigating surgery versus no surgery for proximal phalanx fractures is currently recruiting.
- NIHR HTA: NEON trial investigating repairing or not repairing digital nerve injuries is currently recruiting.
- NIHR HTA: Theseus (Treatment of Hidradenitis Suppurativa Evaluation Study).
- NIHR HTA: SIPS (Surgical interventions to treat severe pressure sores).
- NIHR DRF (Oxford): Hawaii pilot study of antimicrobial versus standard sutures for reducing surgical site infection.
- NIHR DRF (Leeds): investigating major peripheral nerve injuries.
- NIHR DRF (Nottingham): investigating metacarpal fracture management.
- NIHR HTA: FIRST trial investigating rehabilitation following flexor tendon repair.
- NIHR HTA: FLARE trial investigating the surgical management of digital flexor tendon injuries.

A study on antibiotics for simple hand lacerations was highlighted by the NIHR Dissemination Centre. Recent commissioned calls in progress are for cubital tunnel syndrome and thumb base osteoarthritis.

Cardiothoracic surgery

The UK is central to the development of high quality evidence in cardiothoracic surgery through the leadership of international consortia, recruitment of high volumes of people to trials of interventions and the conduct of unique, multicentre, trials funded by the NIHR and British research charities. The examples given below provide some examples of trials that have impacted directly on clinical guidelines and practice.

Key NIHR-funded randomised trials and grants completed 2012–2022

- Transcatheter aortic valve implantation (TAVI) is non-inferior to surgery aged 70 years or older with severe, symptomatic aortic stenosis;[119]
- Video-assisted thoracoscopic lobectomy is superior to open lobectomy in early-stage lung cancer (The VIOLET trial);[120]
- No evidence of long-term survival benefit from the use of bilateral internal thoracic arteries versus a single internal thoracic artery plus saphenous vein, for coronary artery bypass grafting (ARTS Trial);[121]

- No organ protection effect for remote ischaemic preconditioning in high-risk patients undergoing coronary artery bypass grafting (ERICCA Trial);[122]
- No benefit from the use of more restrictive versus more liberal red cell transfusion thresholds in people undergoing cardiac surgery (TITRE2 Trial);[123]
- No benefit for the use of antegrade cerebral perfusion for cerebral protection during surgery with brief (<1h) periods of deep hypothermic circulatory arrest (PEACOG Trial).[124]

Ongoing UK trials

As part of the RCS England Surgical Trials Initiative, UK cardiothoracic surgeons completed a James Lind alliance Priority Setting Partnership (PSP) in Adult heart Surgery.[125] In 2020, this progressed to a new National Cardiac Surgery Clinical trials Initiative, funded by the charity Heart Research UK (https://le.ac.uk/cardiovascular-sciences/about/heart-surgery/national-cardiac-surgery-clinical-trials-initiative). The initiative is co-led in a 1:1:1 ratio by members of the public, clinicians and research methodologists, and has had participation from over 200 stakeholders, including 70 members of the public, over the course of 60 meetings. Thus far, it has established new NIHR-funded research consortia in Surgical Site Infection Prevention and Prehabilitation and multiple funded clinical trials. Central coordination is supported by the BHF Clinical Research Collaborative (https://bhfcrc.org/) and the National Cardiac Surgery PPI Group (https://le.ac.uk/cardiovascular-sciences/about/heart-surgery/national-ppi-group).

An exemplar of patient public involvement is the NIHR-funded DECIDE-TAD programme that is co-led with members of the national patient association Aortic Dissection Awareness in the UK and Ireland (https://aorticdissectionawareness.org/) and has been showcased as a case study of PPI by the General Medical Council. DECIDE TAD aims to develop new targeted screening programmes for people at risk of aortic dissection—a lethal condition that kills more people than traffic accidents per annum in the UK. Current, UK funded, multicentre trials in cardiothoracic surgery include:

- Minimally invasive versus conventional sternotomy for Mitral valve repair funded by the NIHR HTA (UK Mini Mitral, ISRCTN13930454);
- Prevention of dysrhythmias in the cardiac intensive care unit—does maintenance of high-normal serum potassium levels matter? (The TIGHT-K STUDY, NCT04053816) funded by the BHF;
- Nasal high-flow oxygen therapy after cardiac surgery (NOTACS, ISRCTN14092678) funded by the NIHR HTA;
- The Early Valve Replacement in Severe ASYmptomatic Aortic Stenosis Study (EASY-AS, NCT04204915) funded by the BHF;
- Preoperative weight management to improve outcomes of cardiac surgery in adults with obesity (SLIM-CARD): a multicentre feasibility RCT funded by the BHF;
- A multicentre RCT of standard care versus an accelerated care pathway after cardiac surgery funded by the NIHR HTA (FARSTER-care);
- Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery (TRICS-IV, NCT04754022). The UK arm of the trial is funded by the NIHR HTA programme;
- The CO2 study: Carbon dioxide insufflation and brain protection during open-heart surgery funded by the NIHR EME Programme (ISRCTN30671536);
- Efficacy of propofol-supplemented cardioplegia on biomarkers of organ injury in patients having cardiac surgery using cardiopulmonary bypass: propofol cardioplegia for myocardial protection RCT funded by the NIHR EME programme (PROMPT2, ISRCTN15255199).

In addition, UK research networks are recruiting to the following international trials:

- The Randomization of Single vs Multiple Arterial Grafts trial (ROMA, NCT0321700), with funding from the National Heart, Lung, and Blood Institute (NHLBI) and the Canadian Institutes of Health Research (CIHR);
- The Anticoagulation for New-Onset Postoperative Atrial Fibrillation After CABG trial (PACES, NCT04045665) with funding from NHLBI;
- Percutaneous or Surgical Mitral Valve Repair (PRIMARY, NCT05051033) with funding from NHLBI.

Cardiothoracic surgical trainees and allied health professionals have established a new Cardiothoracic Interdisciplinary Research Network (CIRN) to support this programme of trials with Associate Principal Investigators in all UK centres. CIRN also co-leads the NIHR funded consortium TARGET Wound Infection, which is developing a precision medicine approach to wound infection prevention with the UK Health Security Agency.

Ear, nose and throat

UK ear, nose and throat (ENT) surgery has made major contributions to the development of evidence-based practice for the treatment of ENT conditions across the lifespan. Early examples are trials showing clinical benefits for steroids over antivirals for adults with Bell's palsy, and benefits of tonsillectomy in selected children with recurrent sore throat.[126,127] In recent years, UK trials activity in the field has expanded from late phase surgical trials to early phase trials of novel drugs for hearing loss and sinus disease, driven by rapid developments in the understanding of underlying disease processes and identification of therapeutic targets.

Capacity and capability to deliver these trials in ENT services has expanded rapidly through the support offered by the NIHR CRN and will continue to grow by the activities of ENT trainee research collaboratives SFOUK (https://sfo.entuk.org/) and INTEGRATE (https://entintegrate.co.uk/publications).[128]

Completed trials:

- The TOPPITS trial (NIHR HTA) has shown no benefit in the near ubiquitous practice of empirically prescribing proton-pump inhibitors for patients with chronic laryngopharyngeal symptoms. PMID: 33414239; PMCID: PMC7789994.[129]
- The NATTINA trial (NIHR HTA) recently assessed the benefits of tonsillectomy for adults with recurrent sore throat; publication of the trial results is pending.[130]
- The NAIROS trial (NIHR HTA) recently assessed the benefits of nasal septal surgery for symptoms of nasal obstruction; publication of the results is pending.[131]
- The REGAINphase I-II phase I/II trial (EU Horizon2020) of a novel locally applied drug aimed at regenerating inner ear sensory hair cells has shown that this approach is safe, opening avenues for a radically new approach to hearing loss; publication of the trial results is pending.[9,132]
- Commercially sponsored NIHR CRN supported trials of biologicals for adults with severe chronic rhinosinusitis with polyps have shown benefit when added to daily standard of care.[133]

Trials in progress include:

- The MACRO trial (NIHR PGfAR) compared the benefits of surgical and medical management of chronic rhinosinusitis.[134]
- The EVEREST-HN trial (NIHR PGfAR) aimed at developing a patient-reported symptom-based risk stratification system to improve the care of suspected head and neck cancer referrals, started in 2022.[135]

Oral and maxillofacial surgery

UK oral and maxillofacial (OMF) surgery (OMFS) has been at the forefront of many successful clinical innovations in the subspecialties of trauma, temporomandibular joint disorders, precancer, cancer, orthognathic surgery and infection over the last four decades. These have often involved using more sophisticated technology and equipment, usually associated with increased treatment costs.

The advances have been accompanied by many single-centre research studies, reporting mainly on the new treatment without necessarily comparing it with the previous 'gold standard'. Some more enlightened OMF surgeons have conducted prospective randomised studies in their unit to test novel against previous treatment. However, these rarely recruited sufficient numbers to provide definitive answers to the relative clinical value of the novel treatment compared with the previous old-style treatment and almost none included translational elements such as cost effectiveness.

As a result, we have been left with many clinical conditions where there are several treatment options and no evidence for which treatment works best irrespective of the surgeons performing it; or which is less morbid; or which has better quality of life outcomes; or which is less costly. OMF surgeons have always been reassured by the high percentage of success with the treatment they prefer and have not wanted to test whether another option might be better. In fact, many of them presented the view that it was unethical for them to participate in a prospective randomised trial in which they did not believe that one of the arms was as good as the other that they used, despite the fact that half the surgeons in the world were using the other treatment with good results.

Another result of this OMF surgical behaviour is that, in some cases, the novel treatments have become standard custom and practice without any evidence to support their monopoly.

There have been two further problems in our specialty militating against nationwide pragmatic clinical trials. These are the lack of experience of clinical research in our membership and, more significantly, a reluctance of surgeons to collaborate with each other and create nationwide pragmatic trials, the results of which would have impact around the world. These are the negative aspects of OMFS clinical research.

On the positive side, in every OMF condition there is equipoise between OMF surgeons as to how that condition should be treated, and even 'internal' equipoise with a surgeon deciding to manage the same condition differently from one day to the next with no obvious logic to justify their different decisions. In other words there are so many clinical questions to answer that we are 'sitting on a goldmine' of potential pragmatic trials in every aspect of OMFS. And we have a few examples of successfully completed nationwide pragmatic studies and a younger generation of OMF surgeons who recognise the value of clinical research and are keen to set up, or just participate in, nationwide trials.

The first OMFS nationwide purely surgical prospective study compared two vastly different treatments for early mouth cancer and recruited its first patient in 2007. It included studies on quality of life, resource use and complications, as well as overall and disease-free survival. It was half funded by CRUK. As a starting point along the road to clinical trials success, it was probably far too ambitious but it did succeed in introducing 68 surgeons to patient recruitment, 27 of these to acting as PIs, and resulted in a 2019 seminal paper that is defining practice worldwide.

Since then there have been several OMF surgeon-led NIHR-funded multicentre studies on radiation damage, using intraoperative markers to aid cancer resection and a trial of novel agents to reduce postoperative haemorrhage. NIHR also funded the multifaceted Head and Neck 5000 project, which continues to generate important information to the present day.

In early 2021, the British Association of Oral and Maxillofacial Surgeons (BAOMS) research lead worked with Professor Peter Hutchinson to suggest four topics to the HTA that merited clinical research. They asked him to pursue and advise in more detail on two of these and he succeeded in convincing them to generate two calls: a prospective randomised study on mandible fractures and antibiotic stewardship, and the use of Botox in myofascial pain. Our Trainees group MTREC, 1 year after saying they were not ready to do a prospective randomised trial, have now successfully passed the HTA first stage of the antibiotic mandibular fracture trial led by two new co-CIs. We are now suggesting to the HTA that the Botox trial should be recalled, revised and resubmitted in the light of a 2022 systematic review that suggests long-term harm to mandibular bone with Botox treatment.

Thus, although it has lagged behind other surgical specialties, UK OMFS is slowly but surely marching forward from a single CI in 2007 to at least eight CIs now and the prospect of many more trials that improve patient treatment coming in the next few years.

- SEND 2007–2015 active recruitment. Now in follow-up. The SEND (Selective Elective Neck Dissection) study compared two standard treatments for early mouth cancer in a prospective randomised study. It remains the only nationwide multicentre prospective randomised study comparing two different surgical protocols for any head and neck cancer or oral and maxillofacial condition. It recruited 25 new PI and one new CI. A total of 68 UK surgeons treated 614 patients at 27 UK hospitals. In 2019, the British Journal of Cancer reported on the results of its randomised trial, the trial's separate real-world study of the patients who were not randomised but used as a comparator, and the study's meta-analysis of all five previous prospective randomised trials and its own data showing a 31% reduction in the risk of death with SEND.[136] The study also evaluated functional, social and emotional outcomes such as speech, eating and appearance, and resource use. There was no significant difference for these factors between the two treatments. Blood and tissue have been banked for later analysis to investigate the relationship between genetics and patient outcomes. As a nationwide multicentre study with many diversely trained surgeons, its findings are applicable for all surgeons worldwide. The paper has been viewed by over 10,000 people and institutions across five continents and has been cited in 56 articles or books since 2020. The results have already prompted:

1. A new Cochrane review;
2. A pan-European position paper promoting its recommendations;
3. A President of the UICC (Union for International Cancer Control) letter to the *British Journal of Cancer* especially praising the quality-of-life and resource-use research, and finishing with 'irrefutable evidence in favour of END';[137]
4. In April 2021, a commissioned paper for the *Journal of the National Comprehensive Cancer Network USA* entitled 'Time for a change in guidelines' has been downloaded or read in full over 2,000 times.[138]

- HOPON—Hyperbaric oxygen efficacy in ORN. Patients who have received radiotherapy to their jaws during treatment for head and neck cancer are at risk of a condition called osteoradionecrosis, often requiring prolonged and complex surgical treatment. This study measures the value of high pressure oxygen therapy in reducing this risk. Trial completed four articles from 2016 to 2022: three by Richard Shaw et al, and one by Forner et al.[139–142]
- TITAN—Trial of induction TPF in advanced head and neck cancer. TITAN addresses the potential survival advantage of TPF-induced chemotherapy (T, taxane; P, platinum, F, fluorouracil) before surgery and radiotherapy for locally advanced, resectable, squamous cell carcinoma of the head and neck.
- LIHNCS—A multicentre RCT assessing the effectiveness of Lugol's Iodine to assist excision of moderate dysplasia, severe dysplasia and carcinoma in situ at mucosal resection margin of oral and oropharyngeal squamous cell carcinoma. One paper in trials in 2013.[143]
- HEAD AND NECK 5000—To describe the social, lifestyle and clinical features of individuals with head and neck cancer and relate these to outcomes (in terms of morbidity, mortality and quality of life) and to examine the impact of different models of care on outcome and cost of care. They established a large prospective clinical cohort in people with head and neck cancer as a biomedical resource. Between 2014 and 2022, 12 articles have been published with many 'outsiders' allowed to access the data in their area of expertise and publish interesting findings.[144–155]

Neurosurgery

UK Neurosurgery is recognised as a major contributor to RCTs internationally, particularly in the context of the number of neurosurgeons per 100,000 population. Over the past decade, there have been completed trials in trauma, vascular, cerebrospinal fluid/hydrocephalus and spinal neurosurgery. The neurosurgery trial portfolio continues to grow, with open trials across all subspeciality areas. The British Neurosurgical Trainee Research Collaborative (BNTRC) is recognised as a globally leading national specialty collaborative and has led the conduct of two NIHR HTA-funded randomised trials in the field of emergency neurosurgery (RESCUE-ASDH and Dex-CSDH). The Society for British Neurological Surgeons (SBNS) Academic Committee also helps to facilitate the development of new trials. Overall, UK-led neurosurgery trials have provided Class I evidence leading to a change in clinical practice that has improved the treatment and patient outcomes across a range of neurosurgical conditions. Major completed and in progress trials with their outputs include:

Completed:

- The ISAT trial randomised 2,143 patients with ruptured intracranial aneurysms to coiling or clipping. Coiling led to an improvement in outcomes and is now standard of care in the UK.[156]
- The STICH trials have defined the surgical indications for patients with spontaneous intracerebral haemorrhage.[157,158]
- The STASH trial found that statins are not useful in the prevention of vasospasm following subarachnoid haemorrhage.[159]
- The STITCH-Trauma trial found that early surgery reduces mortality for traumatic intracerebral haemorrhage.157
- The RESCUEicp trial showed reduced mortality from surgery (decompressive craniectomy) compared with ongoing medical management for patients with severe, posttraumatic intracranial hypertension, and delineated the range of outcome in terms of recovery/disability in survivors.[160]
- The BASICS trial randomised 1,605 patients and demonstrated a reduction in the risk of shunt infection with antibiotic impregnated shunts compared with standard and silver impregnated shunts. Antibiotic shunts are now standard of care in the UK with an estimated £6 million saving in NHS care costs from avoided infections.[161]
- The BNTRC-led Dex-CSDH trial showed that steroids should not be used in the management of patients with chronic subdural haematoma.[162]

- The NERVES trial showed that nerve root injection was more effective for controlling sciatica than surgery.[163]
- RESCUE-ASDH randomised 463 patients to determine whether bone flap removal improves outcomes in patients with traumatic acute subdural haematoma. The study is completed and the results were published in 2023.[164]

In progress NIHR trials:

- ROAM randomised 157 patients to observation or radiation after surgical resection of atypical meningioma. This very rare tumour required the study to be open in 59 centres across ten countries and will report in 2026.[165]
- SCiL is recruiting patients with subarachnoid haemorrhage to determine if interleukin-1 receptor antagonist reduces vasospasm and improves patient outcomes (https://fundingawards.nihr.ac.uk/award/14/209/07).
- SPRING is recruiting patients undergoing surgery for glioma to determine the role of prophylactic anti-epileptic drugs in seizure prevention (https://fundingawards.nihr.ac.uk/award/16/31/136).
- MAST is currently recruiting patients with traumatic brain injury to determine the role of prophylactic anti-epileptic drugs and the duration of treatment (https://fundingawards.nihr.ac.uk/award/NIHR128226).
- STOP 'EM will determine the role of prophylactic anti-epileptic drugs in meningioma surgery and will randomise 1,004 patients across the UK (https://fundingawards.nihr.ac.uk/award/NIHR129748).
- DISCUS will randomise patients with traumatic spinal cord injury to standard laminectomy or laminectomy with duroplasty (https://fundingawards.nihr.ac.uk/award/NIHR130048).
- DENS will determine the optimal management of elderly patients with C2 PEG fractures (https://fundingawards.nihr.ac.uk/award/NIHR131118).
- CARE will randomised patients with intracranial cavernoma to determine whether conservative or active treatment (surgery or radiosurgery) leads to the improved outcomes (https://fundingawards.nihr.ac.uk/award/NIHR128694).

Transplantation

Several recent randomised trials in transplantation with substantial UK contribution have achieved publication in high-impact journals within the last four years: these include studies in normothermic liver and kidney perfusion (*Nature, Nature Communications, Lancet, JAMA Surgery*).

Currently active transplant trials cover a wide range of targets:

- A recently completed (EVNP) 400-patient trial tests the effect of a brief period of normothermic machine perfusion on immediate graft function after kidney transplantation.[166]
- In the Signet Trial, 2,600 donors will be randomised to receive a statin/placebo to test the effect on organ outcome.
- In the Pithia Trial, the benefit of real-time availability of renal histopathology for donor. Organ assessment is being tested using a stepped wedge-cluster randomised design.
- In the Pluto Trial, the effect is being assessed of Plasma-Lyte on post-kidney-transplant hyponatraemia in children.
- In the Twist Trial, the benefit of subcutaneous wound drains is being tested in high-body mass index kidney transplant recipients.
- In the PLUS Trial, the effect of normothermic machine perfusion of the liver on donor organ utilisation will be tested using a threshold-crossing design.
- In the DeFat Trial, the benefit of fat-removing interventions during normothermic machine perfusion in steatotic livers will be assessed.

Further studies include vascular access interventions:

- The Cobalt Trial is examining whether arteriovenous fistulae should be ligated after successful kidney transplantation.
- The Sonar Trial which tests the utility of ultrasound in the surveillance of arteriovenous fistulae.

Other RCS England research initiatives

In addition to the Clinical Trials Initiative, RCS England run other clinical research initiatives including Global Surgery (RCS England collaboration between the NIHR Global Surgery Unit in Birmingham, and NIHR Research Groups on Global Surgical Technologies (Leeds), Neurotrauma (Cambridge), Postconflict trauma (Imperial) and Burns (Swansea)). RCS England runs a Covid Research Group with over 50 projects looking at the impact of COVID-19 on surgical patients and surgical services, and work with the Future of Surgery Commission researches new technologies including Robotics through the RCS England Radar Group.

Future plans and initiatives

Future plans for RCS England clinical research include an expansion of the trials initiative through the current infrastructure and with further appointments of SSLs and Surgical Trial Centres, growing global surgery with the NIHR and a new collaboration with the London School of Economics (Global Surgery Policy Unit). We are creating a Device Science and Registry Group, which will include the concept of registry embedded trials. Working with the Learning Department is providing opportunities for new modules and courses. Finally, we are developing links with scientists through a buddying scheme: the concept of surgeon in the laboratory and scientist in the theatre to improve the understanding of the relationship between the pathophysiology of surgical diseases and the way they are treated.

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