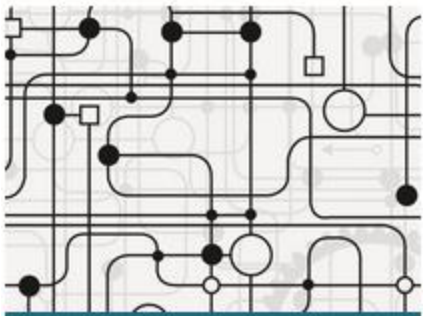
MRC | Hubs for Trials Methodology Research

Improving Health by Improving Trials



Final report 2014-2019

Chair's statement

On behalf of the MRC HTMR Network Executive Committee, it gives me great pleasure to present our final report. We thank the MRC for their recognition that the area of trials methodology was of key strategic importance and their foresight that a network approach would be an effective means to deliver this research. We believe that this investment has provided value for money, and hope our report demonstrates this.

Our eight Working Groups have continued to have autonomy to manage their activities, undertaking new strategic projects funded through our Project Grant Scheme. Members have developed novel designs, core outcome sets, recruitment strategies, and reporting guidelines, collaborating with clinical trialists to improve the design, conduct, analysis and reporting of new studies. Cross-cutting methodological advances have underpinned significant changes to the design and conduct of RCTs in surgery and invasive procedures, in areas including trial recruitment into difficult trials, complex intervention design and delivery, outcome selection, measurement and reporting and methods to optimise trainees' understanding and experience of evidence based practice.

We have disseminated our research in over 130 journal publications, whilst also launching a 'Guidance Pack' available on the Network website (with over 1000 hits per year since 2015) and incorporated into the NIHR Clinical Trials Toolkit. The HTMR Network has increased its visibility through redevelopment of its website, the launch of a Twitter account, and a monthly newsletter collating information on research activity and events. Importantly, we recognised that dissemination was not sufficient to achieve implementation and created a scheme funding impact activities related to 12 Network projects.

Our flagship International Clinical Trials Methodology Conference (ICTMC) has been held biennially between 2011 and 2019, and has become the leading international platform for researchers and practitioners to present the very latest in trials methodology research. Each meeting has grown in delegate numbers, abstract submissions and international reach, and now hosts the Doug Altman Memorial Lecture.

The HTMR Network funded a cohort of 20 PhD students with supervisors from more than one hub. To date, ten graduates have been awarded their PhD and entered employment relating to trials methodology research. Training symposia, internships, networking and other opportunities were available, and the interconnection between different universities in the UK was reported by the students to be "*invaluable to trials methodology research*".

The Network has engaged with relevant stakeholders. Of particular note is the praise and support from Professor Hywel Williams, Director of the NIHR HTA programme, 2015-2020, who said "*I have valued the work that has been done by the MRC HTMR greatly, and I have not been shy in highlighting the specific ways in which your methodological developments have helped the development and delivery of high quality clinical trials for the NHS.*"

The MRC HTMR Network has established the UK as a world leader in trials methodology research. We are thus delighted to report the subsequent creation of the MRC/NIHR Trials Methodology Research Partnership, a larger network of organisations and universities, to allow broader horizon scanning, agility to create groups in new areas, and a whole system approach for both undertaking novel research and achieving implementation in practice.

Paula R Williamson, Chair of the MRC HTMR Network (2012-2014, 2016-2019)

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1. Mission and Structure 2014-2019

Mission

To promote and encourage collaborative methodological research relevant to trials and to enable implementation of the most effective and appropriate methods to improve the quality of trials and, ultimately, patient care.

Executive Committee

Professor Jane Blazeby
Professor Louise Bowman
Professor Will Hollingworth
Mrs Carol Knott
Professor Adrian Mander
Professor Tony Marson
Professor Matthew Sydes
Professor Jayne Tierney
Professor James Wason
Professor Paula Williamson

Dr Sam Rowley (MRC Head Office)

Network Coordinator

Dr Emma Tomlinson (2012-2016)
Mrs Karen Hughes (2016-2017)
Dr Gill Cooper (2017-2019)

International Advisory Group

Professor John Alexander
Professor Deborah Ashby
Professor Isabelle Boutron
Professor Marion Campbell

Organisation

The Network united a cohort of researchers based in five regional Hubs across the UK undertaking research in trials methodology.

The Network was managed by an Executive Committee. It received independent oversight from an International Advisory Group (IAG) which met in June 2015 and October 2017 to advise the Network on objectives and discuss strategic focus.

The Executive Committee included two senior representatives from each hub.

5 Hubs

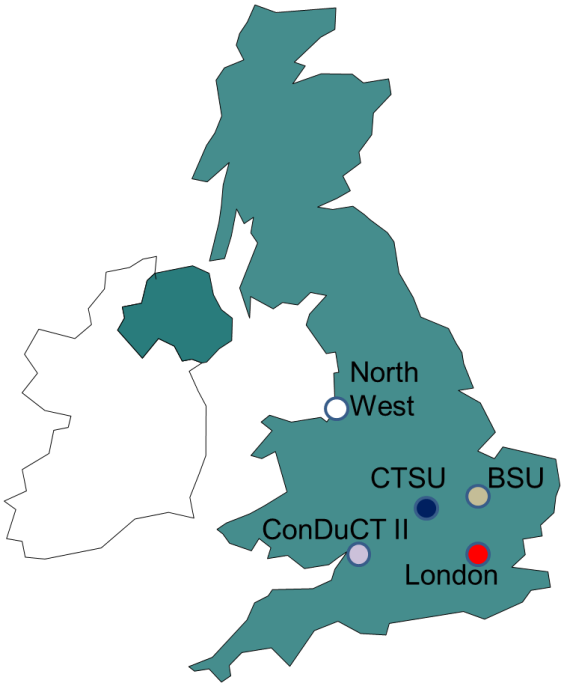
20 PhD students

5 International conferences

25 Network Award projects

12 Network Impact projects

www.methodologyhubs.mrc.ac.uk



Working Groups

Working Groups were set up in areas of strategic importance to clinical trials methodology research:

- Adaptive Design
- Evidence Synthesis
- Health Economics
- Health Informatics
- Outcomes
- Stratified Medicine
- Recruitment
- Trial Conduct

2. Achievements

2.1 Scientific progress

2.1i Outputs

2.1i.a MRC HTMR Network Project Grant Awards

The HTMR Network project funding scheme created a unique opportunity for researchers within the five Hubs to undertake pilot work or developmental projects in trials methodology research which could not be easily supported through other funding streams. The infrastructure of the MRC HTMR Network and the availability of funding awards (of up to £50,000) enabled an efficient and cost-effective approach to successfully delivering research from a UK wide group of expert trials methodologists. The scheme also enabled many Early Career Researchers to gain their first experience of leading research projects. All HTMR Network award applications were peer reviewed by external reviewers.

In 2013, a priority setting exercise was undertaken (Tudur Smith et al., 2014) by several leading members of the HTMR Network. This was the first piece of work of its kind and proposed a trials methodology research agenda, identifying priority topics. Recruitment, retention and choosing appropriate outcomes were identified by consensus as the top three priorities needing further research. This work influenced the HTMR Network funded projects ORRCA I, ORRCA II and COMET, and motivated three further prioritisation projects:

(i) The HTMR Network-funded METHODICAL study which identified Public and Patient Involvement methodological research priorities
(ii) The PRioRiTy studies funded by the Health Research Board with support from the James Lind Alliance - PRioRiTy I which identified priorities for improving the process of trial recruitment and PRioRiTy II which identified priorities for improving trial retention
(iii) A HTMR Network-funded research project which carried out a priority setting exercise in 2017 to outline the foundations of a global health trials methodological research agenda to increase and improve trials in low and middle income countries (Rosala-Hallas et al. 2018)

Between 2014-2019, 25 project funding awards were made (total spend £532,000), covering a diverse range of trials methodology topics and facilitating further collaborations both between the Hubs and strengthening links with colleagues outside the MRC HTMR Network. All awards from 2014 are listed in Appendix 3.These small funding awards developed valuable resources including databases, repositories, online resource platforms, electronic tools and software to aid trial design and analysis. The scheme has also provided complementary funding to support associated projects supported from other sources.

In 2018 the MRC HTMR Network recognised a need to further consolidate achievements of several previously funded projects to maximise their impact or identify how particular HTMR Network research strengths could be further advanced in a planned application for a new partnership (see section 5). In total, twelve impact awards were funded (total spend £58,000) and are described in Appendix 4.

2.1i.b Network Project Outputs

Over 130 peer reviewed publications resulted from MRC HTMR Network funded research and collaborations (Appendix 1). The scheme was highly successful with the following highlighted results (amongst many others):

2.1i.b.1 Adaptive Designs

The Adaptive Designs Working Group was one of the first working groups to be established and continued throughout the duration of the HTMR Network. Its core activity has been to support and facilitate the use of adaptive clinical trials in situations where they are appropriate. A multi-faceted approach that involved writing tutorial papers; training of end-users through outreach visits; actively support implementation of adaptive clinical trials; development of software and guidance (Magirr et al., 2012; Wason et al., 2014; Pallmann et al., 2020), has been taken.

Specifically, two tutorial papers (Pallmann et al., 2018; Wheeler et al., 2019) have been written and published in high impact journals. Despite the first only being published in 2018, Pallman et al. (2018) has been cited 64 times[1]. To supplement the promotion of adaptive designs through scientific publications, the working group also conducted outreach visits to end users. To this end 16 CTUs have been visited and several workshops (e.g. at ICTMC and the NIHR Statistics Group meeting) have been delivered. The working group has actively engaged as co-Investigators or consultants and provided numerous instances of informal support on specific trials – often triggered by the outreach visits. Furthermore the group has developed fit for purpose statistical designs such as the design for the TAiLoR trial (Pushpakom et al., 2020) where the statistical methods papers (Magirr et al., 2012; Wason et al., 2014) have now been cited 65 and 33 times respectively[1].

To enable wider uptake of novel methods, software (e.g. Pallmann et al., 2020; Jaki et al., 2019) has been developed. The MODEST software has been used in the design of new trials, for example in a phase Ib/IIa study to evaluate the safety, tolerability, PK, drug-drug interaction and bactericidal activity of BTZ-043 in participants with newly diagnosed pulmonary tuberculosis, https://clinicaltrials.gov/ct2/show/NCT04044001.

To ensure good reporting, a CONSORT extension for adaptive designs has been developed (Dimairo et al., 2020). This extension was part-funded by a HTMR Network project award, in collaboration with NIHR.

2.1i.b.2 Evidence Synthesis

Activities of the Evidence Synthesis Working Group focussed on research to improve the use of evidence synthesis in the design, conduct, analysis and reporting of randomised controlled trials and to improve the suitability of trial reports for subsequent use in evidence synthesis. Key achievements include (i) the PhD-student led INVEST (INVestigating the use of Evidence Synthesis in the design and analysis of clinical Trials) survey to summarise the current use of evidence synthesis in trial design and analysis (Clayton et al., 2017), (ii) a series of papers on the role of individual participant data (IPD) evidence synthesis in clinical trials (Tierney et al., 2015ab; Vale et al., 2015), (iii) and input into the revised Cochrane Risk of Bias Tool (Sterne et al., 2019).

[1]Figures based on Web of Science. 22nd September 2020

2.1i.b.3 Health Economics

The Database of Instruments for Resource-Use Measurement (www.DIRUM.org) catalogues 94 questionnaires and diaries used in trial-based economic evaluations. DIRUM has been cited 115 times in trial protocols, reports and publications indicating its utilisation in clinical trial research. The DIRUM website is signposted from all regional NIHR Research Design Services.

Related HTMR Network-funded research activities include the development of a standardised resource-use measure (ISRUM), and a modular resource-use questionnaire for use in RCTs (MODRUM), and which progressed to international collaboration on the EU H2020 funded PECUNIA project (https://pecunia-project.eu/). Led by the Medizinische Universität Wien, PECUNIA is developing a standardised, harmonised and validated multi-sectoral resource use measure for use in international health economic evaluations.

Health Economics Analysis Plans (HEAPs) are necessary for transparent reporting of trial-based economic evaluations. Projects funded by the HTMR Network led to the development of a standardised HEAP template, which is now being utilised in several NIHR-funded RCTs.

Methodological development in economic evaluation during early-phase clinical research of pharmaceuticals has been undertaken in collaboration with Pfizer to integrate pharmacometrics with pharmacoeconomics. This has led to a series of outputs describing applications during drug development. These include: providing early indications of cost-effectiveness before large-scale trial data become available; directing future research based on the cost of reducing uncertainty; assessing subgroups, dosing schedules, and adherence; informing strategic research and development along with pricing decisions; and estimating the cost-effectiveness of complex pharmaceutical interventions (such as pharmacogenetic testing). Others have recognised the potential for this approach to impact on the field[2].

2.1i.b.4 Health Informatics

The HTMR Network has explored the field of electronic health data via a number of different approaches to identify and explore the challenges and opportunities electronic health data creates for randomised trials. Two recently completed studies (McKay et al., 2020; Lensen et al., 2020) undertaken by HTMR Network researchers reviewed the access and use of routinely collected data in publicly funded randomised clinical trials. The studies report the limitations and challenges of accessing and reporting use of routinely collected data in randomised trials and how these might be overcome in future. The use of routinely collected health data is the theme of six HTMR Network funded PhD studentships.

2.1i.b.5 Outcomes

COMET

The COMET (Core Outcome Measures in Effectiveness Trials) Initiative was established to improve outcome selection while reducing reporting biases. It has become a benchmark for standardising outcomes, making decisions about treatments more robust and ensuring trials are relevant to patients. Notable achievements include the establishment of the COMET database to transform accessibility of COS research and the increased international uptake of Core Outcome Sets (COS) which has reduced unnecessary duplication of COS development. Seven meetings have brought together international researchers working in trial outcomes research and COS.

[2] Srinivasan M, White A, Chaturvedula A, et al., Incorporating Pharmacometrics into Pharmacoeconomic Models: Applications from Drug Development. *Pharmacoeconomics*. 2020 38(10):1031-1042.

Furthermore COMET has been endorsed in the policies and guidance of key organisations responsible for health care decision making including guideline developers (NICE), regulators (Health Research Authority, European Medicines Agency) and public and commercial trial funders (NIHR, various pharmaceutical companies). COMET has direct patient benefits both through improved information and also via its Patient Participation, Involvement and Engagement (PoPPIE) working group which has established a patient voice in COS research.

CONSORT PRO
The CONSORT-PRO extension (Calvert et al., 2013) has been cited 483 times including European Medicines Agency (EMA) guidance. CONSORT-PRO has led to significant improvements in reporting of PRO data (Mercieca-Bebber et al. 2017); helping to ensure that data on patient quality of life and symptoms are reported in a rigorous way that can meaningfully inform patient choice about treatments, regulatory decision-making, clinical guidelines and health policy.

2.1i.b.6 Recruitment

The HTMR Network has helped support trial recruitment research in a number of ways. The HTMR Recruitment Working Group (RWG) and members of the Qualitative Research Integrated within Trials (QuinteT) team, have worked together to identify opportunities for collaboration and access research funding.

Training for recruitment to trials
A collaboration with York's Prometheus SWAT team led to a study to test the feasibility of undertaking a SWAT of a training course for staff recruiting participants into surgical RCTs. Evaluation is currently underway with preliminary findings presented at ICTMC 2019.

Both the QuinteT team and other RWG members sit on the Steering Committee and share their expertise for the HRB-TMRN TRAIN project led by colleagues in the NUI Galway to develop a training intervention for trial recruiters. A recently published systematic review showed limited evidence on the effectiveness of education and training interventions on trial recruitment (Denaley et al., 2019), following on from an earlier systematic review undertaken by QuinteT colleagues (Townsend et al., 2015).

The QuinteT team led a HTMR Network-funded award (followed by a subsequent HTMR Network impact funding award) which was made possible due to collaborations formed through the RWG. In summary, the original award was to develop, deliver and evaluate training courses for recruitment to RCTs. Four workshops were delivered, training a total of 99 surgeons and research nurses who demonstrated an increase in self-confidence in recruiting patients to trials. Outputs included two papers (Townsend et al., 2015; Mills et al., 2018), a poster presentation at ICTMC, and three further workshops to health professionals in the NIHR West of England Clinical Research Network, North Bristol NHS Trust and University Hospital Bristol NHS Foundation Trust. The impact award following on from the original grant refined and advanced training, making it more sustainable, accessible and suitable for a wider audience. The course has now been accepted as a University of Bristol Medical School Short Course following positive feedback from a pilot workshop and will be delivered annually. The HTMR Network-funded impact project also led to six further spin-off recruiter training opportunities in the UK, USA and Sweden for trialists and health professionals.

ORRCA
The ORRCA project was a HTMR Network funded project led by Professor Carrol Gamble (PI) and supported by RWG co-applicants. The project successfully delivered an online searchable database of recruitment research within clinical trials and this was achieved with input from RWG

members into all stages of the project. The use of ORRCA facilitated a literature review on recruitment strategies in RCTs involving unplanned hospital admissions (Rowlands et al., 2018).

With further impact funding from the HTMR Network the ORRCA project has been extended to ORRCA2 which expands the scope of the database to include recruitment and retention. Updates of the ORRCA database and population of ORRCA2 have benefitted from collaborations developed within the recruitment working group and the contribution of members to ORRCA activities.

2.1i.b.7 Stratified Medicine

Stratified Medicine has been an important emerging area in clinical trials methodology and the HTMR Network supported several initiatives in this area. Through the Stratified Medicine Working Group (SMWG), several events were held. A SMWG-organised workshop in 2017 on “Practical Challenges in Biomarker-Guided Trials’ resulted in a guidance paper being published (Antoniou et al. 2019). Earlier teleconference meetings of the SMWG led to a successful application to the MRC MRP entitled “Developing efficient perpetual platform trials to study multiple treatments and multiple biomarkers”. A 2019 SMWG workshop “Identifying priorities for clinical trials methodology to enable stratified medicine” led to a new research agenda that is being taken up by the TMRP SMWG.

The HTMR Network also supported several projects on stratified medicine. A major impact from one such project is the BiGTeD repository of stratified medicine study designs (www.bigted.org). A further hub project on methods for utilising continuous biomarkers in trials led to an MRP application. The first submission of this was unsuccessful but there are plans to consider revamping and resubmitting it after receiving the detailed feedback.

2.1i.b.8 Trial Conduct

Guidance to optimise pilot study design and conduct
The aim of this study was to provide clear guidance for trialists to inform the selection and design of pilot work prior to a definitive main study, and to provide guidance for selection of progression criteria in RCTs with an internal pilot. Decision-making processes regarding progression to a full main trial were reviewed via analysis of a cohort of 57 protocols of trials with an internal pilot funded by the NIHR HTA (Rosala-Hallas et al., 2019). In-depth qualitative interviews were then conducted to explore the views and perceptions of 19 funding body panel representatives (including NIHR HTA/RfPB/EME/PGfAR, CRUK, CSO, ARUK) towards funding pilot work (publication in preparation). Finally, a one-day stakeholder workshop (funding body representatives and clinical trials units) was held to consider key factors in choosing between an external and internal pilot study design. A further publication is in progress which will detail the overall findings of this work, the implications for future practice and offer guidance on the choice of pilot/feasibility study design.

Trial Steering Committees: Updating and redeveloping guidance and terms of reference
Findings from a recently published suite of research on the third oversight committee were utilised to inform guideline revision. In brief, the research included a survey of 38 UK-registered Clinical Trials Units, a review of 264 published trials, observation of 8 third oversight committee meetings and 52 interviews with trialists. A joint workshop was held between the HTMR Network and NIHR in May 2019 to discuss the third oversight committee and published a commentary outlining issues and proposed revisions. It was concluded that a third oversight committee has benefits for oversight and conduct and a revised Charter will facilitate greater standardisation and wider

adoption (Lane et al., 2020). In linked research, a Search for Oversight Statisticians database of statistical expertise was developed to support oversight committees (http://ctrc.liv.ac.uk/Tools/SOS/Home/About).

SWAR and SWAT Repository

The SWAT (Studies Within A Trial) and SWAR (Studies Within A Review) repositories have developed into a unique resource for methodology studies that are embedded in prospective studies (such as randomised trials) and systematic reviews. There are now more than 125 entries across the two repositories, growing at a rate of 10-20 per year, and they have transformed the discoverability of this type of research. Before their creation, people seeking this research faced the very challenging task of trying to find it amidst hundreds of thousands of reports of potential host trials and reviews. The wider use of the terminology has also made it easier for people to identify this type research, simply by calling it a SWAT or SWAR, and the first two Trial Forge guidance papers highlighted it further[3]. The adoption of SWAT by the NIHR HTA Programme, with up to £10,000 available to embed one in a HTA-funded study, and the recognition given to them by Hywel Williams in his farewell video as he stood down as Director of the Programme is further testament to how the investment by the HTMR Network has improved the landscape of methodology research in health care in the UK and beyond.

Guidance for Statistical Analysis Plans (SAP)

The HTMR Network supported a project developing guidance for Statistical Analysis Plans (SAP) published in JAMA (Gamble et al., 2018). The guidance is also cited in a book (Wensing and Grimshaw, 2020[4]) and several commentaries (Kelly et al., 2019; Kirtschig et al., 2019; Li et al., 2018[5]) outlining important elements of trial conduct and is cross referenced in the CONSORT extension statement for adaptive designs (Dimairo et al., 2020). An editorial in the journal Trials, which recommends several routes for publishing SAPs, will be published later in 2020.

2.1i.c The MRC HTMR Network Guidance Pack

https://www.methodologyhubs.mrc.ac.uk/advice/network-guidance

The online MRC HTMR Network Guidance Pack is a valuable resource which brings together key Network outputs which inform and advise on varied aspects of trials methodology. The full Guidance Pack can be found in Appendix 5. The Guidance Pack currently includes 29 entries and will continue to grow as further MRC HTMR Network funded guidance is published.

2.1ii Synergy in resources and infrastructure

Network funded projects

As described above, several resources were developed by Network members collectively (see section 4), and used for various research projects.

[3]Treweek S, Bevan S, Bower P, et al., Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)? *Trials* 2018;19(1):139. Treweek S, Bevan S, Bower P, et al., Trial Forge Guidance 2: how to decide if a further Study Within A Trial (SWAT) is needed. *Trials.* 2020;21:33.

[4] Wensing M and Grimshaw J. Experimental Designs for Evaluation of Implementation Strategies. *Improving Patient Care: The Implementation of Change in Health Care.* 2020: 345-356.

[5] Kelly J, Hounsome B, Lambert G, et al., Ensuring trial conduct is consistent with trial design: assumption is the enemy of quality. *Trials.* 2019; 20: 9. Kirtschig G, Lo S, Batchelor J, et al., Pragmatic trials: lab meets bedside. *Br J Dermatol* 2019; 181: 431-433. Li TJ, Mayo-Wilson E, Fusco N, et al., Caveat emptor: the combined effects of multiplicity and selective reporting. *Trials.* 2018; 19: 6.

Red Hat Group (RHG)
The RHG was formed was at the 2018 COMET VII meeting and brings together a number of international initiatives associated with improving choice of outcomes in health research. Members include: CDISC, Cochrane Skin – Core Outcome Set Initiative (CS-COUSIN), COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN), Outcome MEasures in Rheumatology (OMERACT), McMaster GRADE Centre and Standardised Outcomes in NephroloGy (SONG). By working together the RHG aim to share knowledge and understanding of mechanisms which will promote the development and uptake of Core Outcome Sets (COS) in comparative effectiveness research.

2.1iii Strategic partnerships

The HTMR Network developed strong scientific collaborations with various strategic partner networks:

(i) UK CRC Registered CTU Network

The UK CRC Registered CTU Network is a network of academic clinical trials units, across the UK, which have been assessed against key criteria by an independent panel of experts in clinical trials research. The Network's aims are to develop and share best practice, encourage the promotion of, and act as a voice for the Registered Clinical Trials Units. Joint projects which brought together expertise from both HTMR and CTU networks include the HTMR Network-funded Search for Oversight Statistician (SOS) Database. HTMR Network-funded guidance including 'Good Practice Principles for sharing individual participant data from publicly funded clinical trials' and 'Guidelines for the Content of Statistical Analysis Plans in Clinical Trials' were both developed with and endorsed by the Registered CTU Network.

(ii) Health Research Board–Trials Methodology Research Network

The Health Research Board-Trials Methodology Research Network in Ireland was established in 2014 as an all-island support network aimed at improving the quality, conduct and reporting of randomised trials in Ireland. The network, which is embedded across five Irish Universities, offers support primarily aimed at Investigator led trials, across a suite of activities under the four main pillars of Training and Education, Support, Public Involvement, and Research and Innovation. Since its inception, the Irish network has benefited from excellent collaborative relationships with the HTMR Network, learning from activities across all hubs in the UK. In 2018 the HRB-TMRN led the PRioRiTy I study, which was the first methodological priority setting partnership in collaboration with members from across the HTMR Network, delivering a top ten prioritised list of research questions, which ultimately have set the research agenda for trial recruitment research.

(iii) The Global Health Network

The Global Health Network (TGHN) is a platform to facilitate research by sharing knowledge and methods. In 2016, TGHN actively collaborated on the HTMR Network award project N84, promoting the Delphi survey which identified priorities for the foundations of a global health trials methodology agenda.

In addition, HTMR Network members met with other stakeholder groups to discuss mutual areas of scientific interest:

- In 2017 the HTMR Network Executive met NIHR HTA committee members to identify mutual areas of interest for future collaboration. Collaborative activity which followed this meeting

included (i) HTMR Network representation at a ‘Round Table Divergent Trials’ discussion in September 2018, and (ii) HTMR and NIHR co-funded a Trial Steering Committee workshop in May 2019.
- Meetings were held with AMRC, CRUK, BHF, INVOLVE, NIHR Stats Group, MHRA, RDS, Cochrane, DPFS, and HRA.
- The HTMR Adaptive Designs Outreach Officer visited Roche, AstraZeneca and Phastar.

2.1iv Leveraged funding

Network awards were used to pump-prime projects which were then the focus of larger funding awards. Appendix 6 lists all successful applications since 2014 resulting from Network funding obtained by HTMR members. Of particular note are the large awards related to surgical research, core outcome sets, and applications of novel methods in new trials.

2.2 Training and careers

2.2i Outputs

HTMR Network PhD students have been encouraged to publish their research as it progressed. Their publications are listed in Appendix 1.

2.2ii Synergy in resources and infrastructure

2.2ii.a Workshops

The HTMR Network project and impact funding scheme also created an opportunity to bring together trials methodologists across the UK to deliver specialist training or workshops across a broad spectrum of trials methodology research topics, initially funded by the HTMR Network.

Table 1 outlines training courses which were delivered in conjunction with HTMR Network project and impact funding across a number of trials methodology topic areas. These courses were generally well attended with a number of courses repeated annually. Several courses were delivered at international locations as well as in the UK.

Table 1 Summary of HTMR Network training courses delivered between 2011 and 2019

Training course title	**HTMR Network lead**	**Overview of training**	**Details of courses held [number of attendees]**
Handling missing outcome data in randomised trials	Ian White (Cambridge/UCL)	Exploration and evaluation of methods to analyse trials with missing data	June 2011 [37] March 2012 [19] Nov 2013 [22] (Melbourne) October 2019 [23]
How to be a Good Chief Investigator	Jane Armitage (Oxford)	Interactive workshop to help understanding of what makes a successful trial with presentations from experienced chief investigators, trial funders and trial methodologists	February 2015 [36] September 2015 [33] September 2016 [20] January 2018 [18] November 2019 [18]
Development of Randomised Trial recruitment training	Nicola Mills (Bristol)	To develop and deliver and RCT recruiter training workshops to enhance recruitment and informed consent	Four workshops 2015-2016 [99] March 2019 [20] May 2019 [45] (SCT) October 2019 [18] (ICTMC) Continuing online 2021
Improving the design and analysis of trials for efficacy and mechanisms evaluation	Tom Palmer (Lancaster), Richard Emsley (KCL)	Training days on methods for EME studies	May 2018 [31] May 2019 [22]
Core Outcome Set (COS) development	Paula Williamson (Liverpool), Bridget Young (Liverpool), Jane Blazeby (Bristol)	To increase the understanding of methods to develop Core Outcome Sets including how to involve patients and the public	Held at COMET III –VII meetings June 2013 November 2014 May 2015 November 2016 November 2018
Adaptive designs and multiple testing procedures	James Wason (Cambridge), Adrian Mander (Cambridge)	In conjunction with the Australian Clinical Trials Alliance (ACTA)	Three 2-day workshops in 2019 [78]

2.2ii.b Clinical capacity building

The HTMR Network provided network grants and support for clinicians and trainee clinicians to increase engagement in clinical trials. In addition it provided training in specific areas of trials methodology relevant to clinicians with an academic interest and academic clinicians in training. It did this in collaboration with other funders (e.g. CR UK), professional organisations (e.g. Royal College of Surgeons of England) and with support from individual Hubs and universities.

Clinical engagement
A workshop jointly supported by Cancer Research UK was held twice during the five years. Attended by over 100 oncologists and surgical oncologists the workshop provided updates and oversights of clinical trials and methodologies. The endeavour was a success and there are plans to run this again in the autumn of 2020 hosted in Bristol and supported by TMRP members.

Five 'How to be a Good Chief Investigator' workshops were held in Bristol, Liverpool, Manchester and London over the five years, with a total of 125 attendees. This provided a networking opportunity for mentorship relationships to develop and specific support for clinicians running trials for the first time.

Feedback demonstrated that 94% of participants agreed or strongly agreed that attendance at the workshop had benefitted their working practice, noting lessons learnt about "*Importance of trial marketing. This has strongly influenced how I communicate about my trial(s).*" and "*It clearly covered the expectations of this role. This was very helpful as I was just starting out in this new role.*"

Trials methodology training for clinicians
Two HTMR Network grants funded focussed workshops. The first included about 40 methodologists and surgeons who worked hard to develop guidance for understanding, designing and evaluating surgical intervention protocols in clinical trials. This is a complex area often criticised for the lack of methodological rigour. The workshop combined with an NIHR doctoral fellowship (Blencowe) held in Bristol contributed to several methodological papers and a report. The typology that was developed is now being used in the design of surgical trials. The HTMR Network associated PhD student (Blencowe) was subsequently successful with an MRC Clinician Scientist award which will develop this methodological area further. The second workshop was held for academic clinical lecturers (ACLs) with an interest in clinical trials methodology. Attended by 30 ACLs from a range of specialities this two day event covered key trial design and protocol issues. Trainees worked in groups to develop and present a clinical trial culminating in a successful and fun 'Dragon's Den' session. In a follow-up feedback survey, 12 months after the workshop, 80% of respondents confirmed that they had applied what they had learnt during the workshop in their research or trial applications.

The HTMR Network funded three clinical PhD fellowships.

Katherine Fairhurst, Bristol, completed her PhD fellowship in 2019 and was appointed as a NIHR Academic Clinical Lecturer in June 2020. Below she describes her experiences of being part of the HTMR Network:

"My PhD, awarded in November 2019, gave me the opportunity to explore a formalised clinical academic career, and develop a broad range of quantitative and qualitative research skills with particular relevance to the design and conduct of surgical trials. Networking and teaching opportunities provided by the HTMR Network, not least the brilliant ICTMC conferences, were fantastic experiences which helped to widen my understanding and appreciation of research methodology. Whilst my position as both a surgical trainee and a PhD student within the cohort of

doctoral students was relatively unique, the Network were hugely supportive, inclusive and enthusiastic about my training and career. The opportunities provided by the HTMR Network, have undoubtedly allowed me to build a strong foundation in research methodology, and have led to my successful appointment as an NIHR Academic Clinical Lecturer at the University of Bristol this autumn. I am, therefore, extremely grateful to both the HTMR Network and my supervisors, for the support, guidance, teaching and inspiration that this fellowship opportunity provided at the start of my clinical academic career."

Violeta Razanskaite, Liverpool, is a third year clinical PhD fellow. Here she describes the development opportunities that have been available during her PhD:

"My clinical PhD fellowship studentship was a new and exciting opportunity which allowed me to immerse myself into my specialty area and gain skills and experience in clinical research. My project was funded by the HTMR Network and I became part of the network's PhD student cohort at the time of enrolment. This has undoubtedly enriched my PhD experience as I was able to meet other researchers involved in clinical trials and share my work and experience with fellow PhD students from the beginning right to the end of my PhD journey. As an HTMR student I was able to present my work at the ICTMC conference and attended regular PhD student workshops which were an excellent source of information and research skills training, and a great networking opportunity. Being a part the HTMR Network helped me to disseminate my research to a wide range of healthcare researchers and make useful contacts for my future career as a clinical researcher."

Graham Powell, Liverpool, completed his PhD fellowship in 2018 and returned to Neurology Specialist Registrar training. Here he describes how his research influences his clinical role:

"I completed a MRC HTMR Clinical Fellowship, assessing the use of routinely recorded data in RCTs. I was privileged to attend the annual MRC HTMR meetings and particularly found the dedicated student meetings to be helpful and enjoyable. I was able to discuss similar interest with peers and the networking and collaboration opportunities were invaluable. I have now returned into clinical practice, with an active interest in research and ongoing projects following from the output of my fellowship."

2.2ii.c HTMR Network PhD student cohort

The HTMR Network has funded a cohort of trials methodology PhD students hosted by the regional MRC trials methodology hubs. Each studentship was assigned supervisors from more than one hub, another example of cross hub working. A full report can be found in the Annex 1 document.

Around the training offered to the HTMR Network student cohort, and the value of being in a cohort, they noted:

"*Being part of the HTMR Network PhD cohort gave me the opportunity to learn about a breadth of trials methodology being done across the network including fields that I'd previously had no exposure to.*" Jennifer Thompson, LSHTM

"*I have enjoyed having a group who understand the frustrations and isolation involved in PhD research, and to be able to benchmark progress! It has been very helpful to be able to discuss issues within the cohort and either come up with solutions or simply empathise with each other. The cohort continue to communicate through a WhatsApp group where we share news and areas of opportunity to develop research skills or promote our research."* Heather Catt, Liverpool

"Travelling to Network meetings and associated conferences meant I could be part of a broader peer group; learning from other Network students and understanding the wider context of my own research. I was actively encouraged to widen my horizons and work outside of my host institution." Lydia Emerson, Belfast

"*As well as the opportunity to attend and present my work at international conferences including ICTMC and COMET, being part of the HTMR Network has given me access to invaluable training sessions and I feel that I have benefited from workshops provided by the Network covering important skills, such as networking. Attending the Annual HTMR meetings has allowed me to broaden my awareness of the research happening in trials methodology field beyond my own area.*" Karen Hughes, Liverpool

"*Things come out the blue during a PhD, as 3 years is a long time, but the HTMR Network and peer groups are receptive and encouraging, creating a space that allows for the most optimal outputs and learning experience for their PhD candidates.*" Lauren Bell, LSHTM

"The HTMR Network have supported me to attend the ICTMC 2019 conference and the HTMR Annual Meeting 2018. I was accepted to present my research at the conference and received valuable feedback. Both events also provided me with the opportunity to network with colleagues working in trials methodology and hear interesting talks on trials methodology research." Kirsty Garfield, Bristol

In terms of benefits to their career, they noted:

"*The yearly meetings provided a chance to network with other students and their supervisors, as well as providing access to training that has been useful to accelerate my post-doctoral career.*" Jennifer Thompson, LSHTM

"Funding for my project allowed me to travel extensively to conduct my clinical research at over 40 UK hospitals; and to present my work at both national and international conferences. It was through these unique opportunities that I was able to establish connections with a broad spectrum of researchers whom I now collaborate with in my Research Fellow post at City, University of London." Lydia Emerson, Belfast

"I was able to access valuable peer support from students further ahead in their PhD programme, and benefited from expert advice and guidance from senior colleagues via interactive workshops and training events. Being a member of the HTMR Network helped prepare me for my post-doctoral career by establishing a firm sense of what is involved in being part of a wide and diverse collaborative research community, that is focused on improving trials methodology to improve patient care." Lucy Beasant, Bristol

"*It has been a very good forum for training and future career advice, the hub has been very supportive of us not only thinking about the present but also our futures.*" Charlie Harper, Oxford

"*I have found participation in the HTMR Network to be incredibly useful and believe it has established a researcher cohort that will maintain links into the future. The training sessions on offer have been very useful and I have directly applied the skills I developed to improving my research career.*" Heather Catt, Liverpool

They noted the benefits of meeting others working in a similar area:

"*As a PhD student the network and interconnection between different universities in the UK is invaluable to trial methodology research. A good example of this is that due to the HTMR network I*

was able to meet another PhD student (Graham Powell) who was conducting research in a similar area to me, and was able to discuss ideas and challenges that helped the direction of my own research." Charlie Harper, Oxford

"*During the PhD, I have been privileged to work with an outstanding team of trials methodologists and behaviour change scientists, all which would not be possible without the support of the HTMR Network.*" Lauren Bell, LSHTM

"The annual training meetings were useful to talk to students at other institutions and those at different stages of their degrees and gave me the opportunity to learn more about trials methodology as a whole. Networking can seem a bit daunting at the start of your career, so the opportunity to meet with other HTMR Network students at conferences made it a lot easier, and the events around ICTMC gave us all a chance to catch up. The experiences provided by the HTMR Network during my D.Phil. have shaped my career and I now work in the area of trials methodology as a Research Fellow at Kings College London." Danielle Edwards, Oxford

2.2iii Strategic partnerships

Two PhD students organised funded internships in industry: Gemma Clayton (Novartis), Daniel Hill-McManus (Pfizer). They noted substantial benefits from the opportunity:

"*During the second year of my PhD, the hub supported my three-month research internship at Novartis in Basel. I used Bayesian multilevel modelling to estimate the incidence of safety events, from a large collection of placebo arm data in first in human studies. Whilst there, I learnt to program in R, enabling greater flexibility for me to switch between different software such as R, Stata and WinBUGS, depending on which is most suitable. I have since published this work in Clinical and Translation Science on which I am lead author.*" Gemma Clayton, Bristol

"During the final year of my MRC Network of Hubs for Trials Methodology Research studentship I spent three months within Pfizer's Global Pharmacometrics group at their site in Sandwich, Kent. During this time, I had the opportunity to conduct some analyses of data from a clinical trial of an active developmental compound. Supported by both the MRC and Pfizer, I also spent a week visiting some Pfizer R&D sites on the east coast of the US. The greatest benefit to me from this experience were the insights it provided regarding the workings of the pharmaceutical industry and the way in which drug development projects are managed. This was especially valuable in the construction of my thesis and journal publications, since the methodology that was the focus of my research is applicable within drug development. The collaboration with Pfizer's Pharmacometrics group has continued beyond my PhD studentship and we have recently submitted a further manuscript for publication." Daniel Hill-McManus, Bangor

Nicola Farrar was awarded travel funding to support study visits to the Qualitative Research in Trials Centre (QUEST) in Ireland, and noted:

"During Spring 2019 I was able to spend some time at NUI Galway thanks to a MRC HTMR Network Internship I was awarded to undertake a qualitative evidence synthesis in collaboration with the QUEST team. Whilst in Galway I received a great deal of feedback and support for the development of my synthesis, in particular help with the search strategy and sampling techniques. It was so valuable to spend time with a group with so much experience undertaking evidence syntheses, and to build the connections for when I returned home. Since my visit, I've continued to work on my evidence synthesis alongside my primary PhD data collection, and am currently in the

process of submitting the protocol paper for publication. The synthesis will form a key part of my thesis, and brings a new angle to my research." Nicola Farrar, Bristol

2.2iv Leveraged funding

Several HTMR Network members were successful in obtaining training and career development fellowships, including:

- Howard Thom (Bristol) - awarded a MRC New Investigator Research Grant in 2019 following Network award N79
- Claire Planner (Manchester) - awarded a NIHR School for Primary Care Research Fellowship following Network award R46
- Natalie Blencowe (Bristol) - awarded an MRC Clinician Scientist Fellowship following Network award R29
- Beth Conroy (Liverpool) - awarded an NIHR Doctoral Fellowship following Network award R29
- Amber Young (Bristol) – awarded an NIHR Doctoral Fellowship following Network award R1
- Karen Coulman (Bristol) – awarded an HEE/NIHR Integrated Clinical Academic Fellowship following Network award R1
- Several other NIHR fellowships have been awarded to clinicians outside of HTMR following advice on core outcome set development from the COMET team (Williamson and Blazeby) during the application stage following Network award R1

2.3 Knowledge transfer and exchange

2.3i Outputs

2.3i.a Citations of journal publications

HTMR Network members were encouraged to publish their work in peer-reviewed journals and actively disseminate the resulting publications. Appendix 2 includes a citation analysis[6] for the 132 articles published between 2014 and 2019 listed in Appendix 1. Figure 1 shows a steep trajectory over the time period. The Network have produced a good number of papers with very high citation rates (Figure 2), including 57 (43%) with 10 or more citations, 15 (11%) with 50 or more, and 6 (5%) cited 100 times or more. A relatively small number, 16 (12%) have not yet been cited however they were published only recently.

Several HTMR Network papers are chapters within the 2019 *Cochrane Handbook for Systematic Reviews of Interventions* (Editors: Higgins, JPT, Thomas J, Chandler J, et al.), which has been cited 587 times[6].

[6] Citation analysis numbers were taken from Web of Science, September 2020.

2.3i.b Network-funded research findings applied in trials

SAP guidance

The HTMR Network supported a project developing guidance for Statistical Analysis Plans (SAP) published in JAMA (Gamble et al., 2018). The SAP guidance has been cited 68 times[7], citations from 2020 indicate the SAPs guidance is being increasingly used as a template. Of the 46 citations in 2020, 19 were published SAPs using the guidance with a further 2 protocols stating the future SAP would comply. In comparison, in 2018 and 2019 combined there were only 15 published SAPs citing the guidance.[7] Between 12th December 2019 and 27th August 2020 the SAP checklist and elaboration document (available from http://LCTC.org.uk and the Equator website) have been downloaded 118 times and 59 times respectively. NIHR/ NETSCC have recently agreed to include the SAP guidance in their new Data Management and Access Plan template.

Uptake of Core Outcome Sets

Examples of impact arising from COMET activities include:
- A body of world-leading outputs seen as an essential point of reference by
(a) Core Outcome Set (COS) developers – citation of our key methodological papers funded by HTMR Network project awards (COS-STAD, COS-STAP, COS-STAR) has increased from 21% (10/48) for all published studies identified in 2017 to 77% (23/30) in 2018;
(b) Trial funders (e.g. NIHR, Horizon2020, DFG Germany, PCORI, KCE), protocol advisors (e.g. SPIRIT, UK Health Research Authority, NIHR Clinical Trials Toolkit), regulatory bodies (EMA, NICE, SBU Sweden) and industry (http://bd4bo.eu/index.php/toolkit/) - see http://www.comet-initiative.org/cosuptake.
- COMET has led to increased patient and public participation in COS development, from 17% before 2013, to 41% by 2019, and now 90% in ongoing studies.
- Winner of the international Cochrane-REWARD prize in 2017 for reducing waste in research.

MAMS and adaptive design guidance

A MAMS guidance paper (Wason et al., 2016)[8] that arose from a HTMR Network award has been cited 33 times[9] and is included in the NIHR Clinical Trials toolkit (http://www.ct-toolkit.ac.uk/routemap/trial-planning-and-design/). Guidance from the paper has been used in design of several MAMS trials, including CONFORM-OH, MIDFUT, and RAPID-I.

A recent guidance paper (Pallmann et al., 2018)[10] which describes the rationale of adaptive designs, as well as how to implement and report them has been cited 66 times[9].

Enhancing recruitment and consent trials with children and young people

Ongoing methodological work on clinical trials with children has influenced guidance and practice to enhance recruitment and consent seeking with children and their families, including RCPCH, NIHR and Nuffield Council on Bioethics and training for Research Ethics Committees. Nationally and internationally the work is contributing to consolidation of a culture change so that children are 'protected *through* research' rather than being 'protected *from* research'.

Children are particularly underrepresented in clinical trials of life saving treatments as research in emergency settings is practically and ethically challenging. Legislation change from 2008 allowed

[7] Figures taken from Web of Science and Google Scholar 25/09/2020
[8] Wason J. Magirr D. Law M. Jaki T. (2016) Some recommendations for multi-arm multi-stage trials. *Statistical Methods in Medical Research* 25: 716-727
[9] Figures taken from Web of Science 26/09/2020
[10] Pallmann P, Bedding AW, Choodari-Oskooei B, et al., Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med.* 2018 28;16(1):29.

paediatric research without prior consent (RWPC). However, by 2015 only one trial had been conducted and considerable uncertainty about the acceptability of RWPC remained. Funding from the MRC HTMR enabled development of CONNECT guidance to provide recommendations on when and how to seek RWPC, including what should happen when a child dies after being randomised to a trial without prior consent (2015-2016). This led onto the subsequent Voices project, which investigated children's views of RWPC and co-designed a child-friendly animation (https://youtu.be/_Fs1yUxeBFQ) to explain critical care research to child participants following their recovery, embedded into recruitment for three trials.[11] [12]

The CONNECT guidelines were included in the NIHR Clinical Trials Toolkit in 2016. Since 2014 there have been eight clinical studies using RWPC and informed by CONNECT guidance. These include: a multi-centre clinical trial (EcLiPSE), three pilot trials (FiSh and Fever exploring treatments for sepsis and OXY-PICU, which explored optimal blood oxygen levels), two diagnostic accuracy studies for conditions such as meningitis (Pic Study, PAT POTS), and one biomarker cohort study (BASIC) to inform the care of critically ill children[13]. To date, these studies nationally have recruited 1017 patients using RWPC. Between 2014 and 2016 CONNECT evidence and guidance was integrated into EcLiPSE trial training on RWPC and delivered to 2,024 practitioners across 30 UK hospitals. EcLiPSE was the first UK Clinical Trial of an Investigational Medicinal Product (CTIMP) since the legislation change. An evaluation of RWPC training[14] demonstrated significantly improved practitioner confidence in explaining the study to parents, including why consent had not been sought before study entry and addressing parents' objections during resuscitation.

2.3i.c Example of Network funded research being endorsed

Data sharing guidance

In 2014, HTMR Network funded research outlined recommendations for clinical trial data sharing following a review of current practices across UK CTUs regarding data access and data sharing. The guidance (Good Practice Principles for Sharing Individual Participant Data from Publicly Funded Clinical Trials, Tudur Smith et al., 2015) has been endorsed by the UK CRC Registered CTU Network, Cancer Research UK, MRC Methodology Research Programme Advisory Group and Wellcome Trust, with support also from NIHR. The guidance was a key contributor to the formation of the UK CRC registered CTU Network Data Sharing Task and Finish Group.

2.3i.d Network Impact Project achievements

Health Economics Analysis Plans (HEAP): Dissemination Workshops

To increase the impact of the HEAP and ensure that it is widely used by professional health economists working on economic evaluations alongside clinical trial, a hands-on training session in

[11] Woolfall, K, Gamble, C, Frith L, the CONNECT Advisory Group and Young, B. (2015) Research without prior consent (deferred consent) in trials investigating the emergency treatment of critically ill children: CONNECT study guidance Version 2.0 https://www.liv.ac.uk/psychology-health-and-society/research/connect/ and manuscript version: Woolfall, K., Frith, L., Dawson, A., Gamble, C, Lyttle M the CONNECT advisory group* and Young B. 15-minute consultation: An evidence based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials. *Archives of Disease in Childhood Education and Practice*. 2015 http://ep.bmj.com/content/101/1/49.long

[12] Roper, L, Sherratt, F, Young, B, et al., Children's views on research without prior consent in emergency situations: a UK qualitative study. *BMJ Open* 2018; 8:e022894. https://bmjopen.bmj.com/content/8/6/e022894

[13] Clinical studies using RWPC informed CONNECT evidence and guidance: https://www.liverpool.ac.uk/population-health-sciences/research/connect/useofconnectguidance/

[14] Woolfall, K, Roper, L, Humphreys, A, et al., Enhancing practitioner confidence in recruitment and consent in the EcLiPSE trial: a mixed method evaluation of practitioner training– a Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) study. *Trials* 20:181 *https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3273-z*

writing a HEAPs was developed and successfully delivered to thirty health economists. The workshop consisted of a mix of practical hands-on sessions and short, targeted lectures. Participants were encouraged bring their own HEAP to work on in the practical sessions with support from expert tutors. Feedback from the workshop indicated that participants particularly valued the opportunity to develop their own HEAP, and to discuss the issues that arose. Over 95% of respondents rated the speakers and practical sessions as good or excellent.

Digital Health Interventions Workshop: Outcomes and Issues to consider document
A Digital Health Interventions workshop was held in December 2019 with 35 researchers in attendance. Several of the workshop attendees have since joined the TMRP Health Informatics working group, one of whom will be presenting at the next working group meeting on the current literature and gaps in knowledge regarding evaluation of digital health interventions. There have also been discussions with MRC representatives with regards to potential avenues for dissemination of the workshop findings, and they alerted us to various relevant funding streams (including a new advisory board on digital health, about which they will keep us informed). The "Issues to consider" document is in final stages of drafting, with a view to publish by November.

ReSurgEnT: Using digital stories to outline strategies for engaging clinical trainees in trials
A link to the digital story 'Engaging surgical trainees in trials' which can be viewed on YouTube (https://youtu.be/vbITEHMjQfU) (325 views Nov 2019-Sept 2020) has been circulated to all participants and stakeholders who took part in the stakeholder workshop. The digital story has also been shared via social media including Twitter (232 twitter impressions) and 16 retweets. Feedback from the digital story has been positive and has been further shared and uploaded by several Trainee Research Collaboratives including SPARTANS and TASMAN in the UK and the Surgical Trainee Organisation for Research Central Coast Collaborative, and SUNRRISE in Australia. The study and digital story was presented at the National Trainee Collaborative Meeting which took place in Newcastle on 6th December 2019.

A collaboration with Southampton Clinical Trials Unit is underway to use the methodology of digital stories to disseminate findings about the use of digital tools in recruitment and retention in trials.

Synthesis of patient and public involvement research findings from a portfolio of HTMR Network projects
HTMR Network impact award funding supported a workshop which aimed to reflect on several HTMR Network funded projects and develop guidance for effective Patient, Public Involvement & Engagement (PPIE) in the context of Trial Methodology Research. Several high priority questions were identified by researchers and key stakeholders during the workshop. A meeting report titled 'Actively Involving Patients/Public with Trials Methodology Research (TMR)' was disseminated across the Trials Methodology Partnership Research Executive, Working Groups and social media.

2.3i.e COMET podcasts and webinars

The COMET Initiative has compiled a collection of podcasts which demonstrate the importance of the development and use of Core Outcome Sets (COS) from a range in a range of different fields. The organisations which presented the podcasts include the International PPI Network, European Medicines Agency and the Irish Neonatal Health Alliance.

On February 27th 2020, the COMET PoPPIE (People and Patient Involvement, Engagement and Participation) Working Group delivered a webinar for the International Patient and Public Involvement Network titled 'No Choice of Outcomes About us Without us!' The audience were largely patient and PPI organisations and the webinar was designed to raise awareness of what

core outcome sets are, how they are developed, how patients and patient organisations can be involved and what is it like for those that get involved. Two patients and a patient organisation gave presentations of COS studies they had been involved with. There were 88 attendees (the largest ever registration for International PPI Network webinars). The webinar received very positive feedback including comments in a BMJ Blog, stating for example "The webinar content was skilfully crafted and made the dry subject of outcome measures come alive. I learnt a lot, as speakers took participants through the rationale for agreeing a minimal set of outcomes for different conditions, how to go about reaching agreement on what the measures should be, and the extent to which patients and patient organisations are involved in co-developing them". The webinar was recorded and is available here.

2.3i.f NIHR Clinical Trials Toolkit

The HTMR Network has contributed to several sections within the NIHR Clinical Trials Toolkit, an interactive roadmap which provides practical advice to researchers in designing and conducting publicly funded clinical trials in the UK. The toolkit references the Guidance Pack and HTMR Network members have co-written several sections based on their expertise and published research.

2.3i.g MRC HTMR Network Communications

A regular newsletter was distributed to around 750 UK and international people, describing HTMR Network achievements and signposted subscribers to valuable sources of information and guidance –supplied from both the HTMR Network and external organisations. The newsletter provided a leading guide to forthcoming training opportunities and conferences of potential benefit to trialists and trials methodologists. An annual newsletter was released to mark International Clinical Trials Day, showcasing the HTMR Network achievements as well as raising awareness of the history of the first recorded clinical trial.

Another successful channel of communication and dissemination is the HTMR Network twitter profile which was launched in 2016 and had gained almost a 1000 followers by the close of 2019. Twitter has proved a highly successful tool to rapidly and widely disseminate outputs and news not only to our followers but also via high levels of retweeting.

2.3i.h MRC HTMR Network Webinar Series

www.methodologyhubs.mrc.ac.uk/resources/webinars

Between 2014-2019, the HTMR Network Trial Conduct Working Group webinar series included 36 webinars covering a wide selection of themes within trial conduct. On average each webinar received 40 live views and webinar recordings are available to watch on YouTube via the HTMR Network website's designated webinar page.

In 2018 a joint seminar series was co-organised by the HTMR Network and the Society for Clinical Trials.

2.3ii Synergy in resources and infrastructure

2.3ii.a International Clinical Trials Methodology Conferences

There have been 5 International Clinical Trials Methodology Conferences (ICTMC) held biennially between 2011 and 2019. The conference has become the leading international platform for researchers and practitioners to present the very latest in trials methodology research. Each meeting has grown in delegate numbers, abstract submissions and international reach (see Table 2).

In 2017, ICTMC joined up with the Society of Clinical Trials which attracted a wider international audience and broader scientific programme. The 6th edition of the meeting will take place in October 2021 with scope to widen accessibility to trials methodology colleagues worldwide through virtual access.

Table 2 illustrates the significant growth in attendance, countries represented and abstract submissions across the 2011-2019 ICTMC meetings. ICTMC meeting location was also rotated across UK regions. Notably, the 2017 joint meeting with SCT attracted a larger and wider international audience, the success of which was in part replicated at ICTMC 2019.

Table 2 ICTMC meetings between 2011-2019: Numbers of delegates and abstract submissions

Year	Location	Number of delegates	Number of countries represented	Number of abstracts accepted	Keynote speakers
2011	Bristol	443	9	171	Peter Sandercock (University of Edinburgh, UK) Stephen Senn (Luxembourg Institute of Health, Luxemburg) Marc Buyse (International Drug Development Institute, Belgium)
2013	Edinburgh	615	11	282	Iain Chalmers (James Lind Alliance, UK) Rory Collins (University of Oxford, UK) David Demets (University of Wisconsin, USA)
2015	Glasgow	638	9	338	Sheena McCormack (MRC at UCL, UK) Peter Horby (University of Oxford, UK)
2017	Liverpool	1060 (joint with SCT)	27	614	Susan Ellenberg (University of Pennsylvania, USA) Hywel Williams (University of Nottingham and NIHR HTA, UK) Michael Gaziano (Harvard University, USA)
2019	Brighton	738	23	528	Marion Campbell (University of Aberdeen, UK) David Beard (University of Oxford, UK) Janet Dancey (Queens University, Ontario, Canada)

ICTMC encourages attendance of Health Care Professionals, PhD students and researchers from low and middle income countries (LMICs), in addition to trialists and trials methodologists.

HTMR Network PhD students were awarded complimentary ICTMC registration (2015, 2017, 2019) as part of their studentship and were encouraged to submit abstracts for oral or poster presentation. An ICTMC PhD social event with opportunity for networking was scheduled as part of the meetings.

An educational programme was introduced from 2017 to cover a broad area of trials methodology topics enabling attendees to learn about the latest developments in clinical trials and trials methodology and widen their expertise.

Internationally recognised researchers are invited to present keynote talks at each conference. In 2019, Marion Campbell presented the inaugural Doug Altman Memorial lecture, titled: ‘The future of the randomised controlled trial in the era of real world evidence”.

Almost all (95%) feedback respondents felt ICTMC 2019 met or exceeded expectations. Four fifths of respondents said the conference gave them practice-shaping or practice-changing knowledge, and five sixths agreed the conference increased their awareness of issues in trials methodology research – methodology issues have been commonly overlooked by most day-to-day trial practitioners. 43% felt the conference was an opportunity to disseminate their research to a new audience.

To raise awareness of trials methodology within LMICs, a competition was held in 2019 in conjunction with The Global Health Network offering free ICTMC registration. The winner was Mercy Chepkirui from Nairobi, Kenya.

The following ICTMC PhD student prizes have been awarded: best oral presentation 2019 (Karen Hughes, University of Liverpool, Exploring the barriers and facilitators to core outcome set (COS) uptake), best poster: 2019 (Annabelle South, MRC CTU, Uptake of interventions to communicate results of a phase III randomised controlled trial to participants: early results from the Show RESPECT study) and best poster 2017 (Matthew Parkes, University of Manchester, The two stage treatment selection (TSTS) design: A novel approach to treatment selection in clinical trials).

Conference exhibitors and invited speakers have included colleagues from industry, med-tech, biomedical, funding bodies and charities.

The abstracts presented at each ICTMC meeting are published in the journal Trials and many have subsequently been published as full papers.

2.3ii.b MRC HTMR Network Annual Meetings

The HTMR Network annual meetings brought together colleagues across all five hubs and provided an opportunity for stakeholders to see the work of the HTMR Network. Meetings were held in 2015 (Bristol), 2016 (Cambridge) and 2018 (London).

2.3iii Strategic partnerships

2.3iii.a UKCRC Registered CTU Network

A HTMR Network update was delivered at each Registered CTU Network Executive and annual CTU Directors' meeting. The quarterly Registered CTU Network newsletter, featured HTMR Network news highlighting Trial Conduct webinars, new publications, ICTMC updates and HTMR PhD cohort news. Several HTMR Network members were also members of the Registered CTU Network Operations and Task and Finish Groups.

2.3iii.b UKTMN

The UK Trial Managers' Network (UKTMN), established in 1998, is a dynamic network of UK Trial Managers working together, sharing knowledge and experience, towards the efficient delivery of clinical trials and well-designed studies. It includes over 900 trial managers from across the UK, including representation from all HTMR Hubs, and provides a forum to promote best practice in effective management and delivery of clinical trials. Since 2014 the activities of the UKTMN have been funded by the University of Oxford's Nuffield Department of Population Health (CTSU Hub). An update on HTMR Network activities was a regular feature of UKTMN newsletters, and HTMR Network members gave presentations at UKTMN annual meetings.

2.3iii.c HDR UK

Health Data Research UK (HDR UK) was founded in 2016 as a multi-funded, national institute for health data science and biomedical informatics research. HDR UK aims to increase and facilitate the availability of heath data to better understand diseases and other human health challenges while researching treatments and tackling health system sustainability. The HTMR Network were represented at a joint HDR UK-CPRD-NIHR workshop about data-enabled trials in 2018. A paper from the workshop is being written up for publication.

2.3iii.d Health Research Board – Trials Methodology Research Network

Since its inception, the Irish network has benefited from excellent collaborative relationships with the HTMR Network, learning from activities across all hubs in the UK. The Irish network, benefited from the high calibre trial methodology expertise which exists across the HTMR Network, and was able to utilise the MAST service, in order to offer support to grant applicants at design stage or trouble shoot more complex trial methodology issues throughout the conduct of a trial. The HRB-TMRN also welcomed members of the HTMR Network to its successful webinar and training events, which to date, have welcomed over 15,000 delegates in six years.

2.3iii.e European Clinical Research Infrastructure Network (ECRIN)

The European Clinical Research Infrastructure Network (ECRIN) is a not-for-profit organisation that supports the conduct of multi-national clinical trials in Europe. ECRIN has actively promoted and disseminated information about the HTMR Network project COMET and hosted a COMET PhD student internship. ECRIN and HTMR members collaborated on the European Union (EU) funded CORBEL (Coordinated Research Infrastructures Building Enduring Life-science Services) programme on a core outcome set work package.

Publication of the HTMR Network data sharing guidance led to an invitation for Catrin Tudur Smith to join a working task expert group of the CORBEL consortium to develop procedures for clinical trial data sharing. The HTMR Network data sharing guidance, along with other relevant guidance at the time, was taken into consideration during a consensus exercise and, as a consequence, was referenced in the report produced[15].

2.3iii.f Australian Clinical Trials Alliance (ACTA)

Members of the Adaptive Designs working group delivered courses during February-March 2019 in Australia. These were organised by the Australian Clinical Trials Alliance (ACTA). Three two-day courses were run in Melbourne, Brisbane and Sydney entitled 'Adaptive Designs and Multiple Testing Procedures'. Over the three courses there were a total of 78 delegates.

2.3iii.g Clinical Trials Transformation Initiative (CTTI)

The Clinical Trials Transformation Initiative (CTTI) aims to develop and drive adoption of practices that will improve the quality and efficiency of clinical trials. Members of the HTMR Network have collaborated with CTTI on various activities including the 'Quality by Design' project (to actively promote high quality approaches to clinical trial streamlining), the launch of the 'MoreTrials' campaign, and together with the University of Oxford China Centre helped foster an environment for tackling obstacles to high-quality clinical trials in China.

2.3iii.h The Global Health Network (TGHN)

The Global Health Network (TGHN) was engaged with the COMET impact project, assisting with publicity of the COMET VII bursary opportunities and helping raise awareness of core outcome sets in LMIC settings.

2.3iii.i Society of Clinical Trials (SCT)

The Society of Clinical Trials (SCT) is an international, multidisciplinary, professional organisation advancing the development and dissemination of research in the design, conduct, analysis and reporting of clinical trials. Members of the HTMR Network Executive delivered a session describing the HTMR Network and its research at the SCT 38th Annual Meeting in 2016. In May 2017, SCT and ICTMC hosted a joint Conference which attracted over 1000 delegates. In 2018 SCT and the HTMR Network compiled a joint seminar series.

[15] Ohmann C, Banzi R, Canham S, et al. Sharing and reuse of individual participant data from clinical trials: principles and recommendations. *BMJ Open* 2017;7:e018647.

2.3iv Leveraged funding

During the HTMR Network funded project R30 (Trial Steering Committees (TSC) for RCTs: Updating and redeveloping Guidance and Terms of Reference) it was identified that there was a need for greater training for TSC Chairs. In 2020, NIHR funding was awarded to HTMR Network members to enable future delivery of a new online workshop “How to run a good Trial Steering Committee” for TSC Chairs of new trials, based on guidance produced from the project.

3. Lessons learned

Given the level of investment in the HTMR Network, it is important to reflect on the past 10 years, and to consider how the trials methodology community as a whole could further increase its value. Some key reflections and recommendations are briefly described.

(i) Achieving impact
Several Network initiatives have achieved substantial impact during the funding period, others are starting to have impact now. Increased emphasis on pathways to impact early on in a project's lifetime is needed, together with funding directed to speed up the process.

(ii) Engaging with stakeholders

Over time the Network has achieved excellent engagement of clinicians, spearheaded by a clinical trials methodologist (Professor Jane Blazeby). Factors increasing engagement included the need to tailor activities to their level, include trainees as well as consultants, deliver workshops locally, and emphasise applied trials methodology.

Engagement with industry has been challenging due to limited connections within the network. The exception to this has been in the area of adaptive designs. In hindsight, we recognise that an industry representative would have been a valuable inclusion on the International Advisory Committee.

(iii) Funding for methods research projects
As a proportion of funding for health research overall, methods research receives very little. The MRC MRP scheme is recognised to fund high quality research but has a limited budget, may not consider aspects of the work described in this report to be within scope, and has an application process not suited to important but low cost projects. The Network project funding scheme was a successful way of delivering low budget, cost effective projects, e.g. ORRCA. We welcome the increased recognition of methods research over recent years by the MRC in particular.

(iv) Building a community
Establishing individual Hubs was an incredible opportunity. Establishing the Network of Hubs was challenging at first but our report shows how valuable it was to do so, with the second round of funding being key to realising the potential. Networks need new members to bring new ideas, and our engagement with the wider UK methodologist community, whilst excellent now, would have benefitted from earlier attention. On the international stage however, the MRC HTMR Network is recognised to be world-leading. ICTMC has helped to realise this ambition, and the Network is a co-applicant on several trials methodology research bids to the EU currently under review.

(v) Horizon scanning
Linking to a broader community can identify initiatives of potential benefit earlier. For example, although links with HDR UK are now strong, our portfolio of health informatics research was initially slow to develop.

(vi) Sustainability
The five inter-related elements described above are essential ingredients of a sustainable system for trials methodology, which is critical for high quality research and thereby improved health. Methodologists should take every opportunity to promote the value of methods research for increasing efficiency and reliability of the research process, and thus reduce research waste. Increased funding for methods research will increase value for money in the health system as a whole.

4. Data/resources legacy

Table 3 describes the electronic resources and tools which were generated by HTMR Network funded projects. The table includes cumulative data on relevant indices (visits, downloads, searches) measured for each resource since its online launch and during the previous 12 months.

- The HTMR Network has identified priority lists for trials methodology research (page 4).
- Guidance has been brought together in an online Pack (page 9).
- Reporting guidelines have been developed in a number of areas: core outcome set development (page 9), CONSORT extensions (pages 5 and 7), statistical analysis plans (page 9), and health economic analysis plans (page 6), data sharing (page 19), and assessing the risk of bias (page 5).
- HTMR Network Trial Conduct webinar series - http://www.methodologyhubs.mrc.ac.uk/resources/webinars/

Table 3 HTMR Network funded electronic resources and overall visitor activity since online launch

Resource	**Description**	**Weblink**	**Activity since website went live**	**Activity during previous 12 months (Sept 2019-Aug 2020)**
BiGTeD (Biomarker-guided trial designs)	Online tool demonstrating key characteristics and methodology of biomarker-guided trial designs	http://www.bigted.org/	Sept 2017 - Aug 2020 Visits: 5657	Visits: 1030
COMET (Core Outcome Measures in Effectiveness Trials)	Searchable database of published and ongoing Core Outcome Sets (COS)	http://www.comet-initiative.org/	Sept 2011-Aug 2020 Visits: 215099 Page views: 486044 Database searches: 44375	Visits: 48246 Page views: 154437 Database searches: 13719
DIRUM	Database of resource-use questionnaires for use by health economists involved in trial-based economic evaluation	http://www.dirum.org/	June 2011- Aug 2020 Resource downloads: 9154 Visits: 19,094 Page views: 106,646	Resource downloads: 1100 Visits: 2128 Page views: 9428
MoDEsT	Web application for designing and conducting single-agent dose-escalation studies	https://modest.lancaster.ac.uk/	Sept 2017- Aug 2020 Software downloads: 17173	Software downloads: 8504
ORBIT	Information source and platform for researchers to apply ORBIT methods by downloading the research tools	http://www.outcome-reporting-bias.org/	July 2016-Sept 2020 Visits: 3792 Page views: 7148	Visits: 1225 Page views: 2377

Resource	Description	Weblink	Activity since website went live	Activity during previous 12 months (Sept 2019-Aug 2020)
ORRCA	Searchable database of trial recruitment and retention literature.	https://www.orrca.org.uk/	Sept 2016- Aug 2020 Database searches: 4397	Database searches: 1200
RoB 2 (Risk of Bias 2)	A framework to consider the risk of bias in the findings of any type of randomized trial	https://www.riskofbias.info/welcome/rob-2-0-tool	Aug 2019- Sept 2020 Page views: 68204	Page views: 57264
SWAT / SWAR repository (Studies Within A Trial/Studies Within A Review)	Searchable platform to showcase ongoing or planned SWAT / SWAR research studies.	https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SSWARInformation/Repositories/SWATStore/	Sept 2015-Aug 2020 SWAT Repository page views: 7696 SWAR Repository page views: 539	SWAT Repository page views: 4005 SWAR Repository page views: 180

5. Future vision

RCTs are now widely recognised as the basis of evidence-based medicine. This is, however, still a young field. The MRC HTMR Network was driven by a need to reach out and connect groups to build capacity and critical mass of expertise. This has been achieved, and other networks and groups are now reaching out to join the body of expertise created. To increase unity and recognition of the trials methodology community, we have formed the MRC/NIHR Trials Methodology Research Partnership (TMRP), comprising: the existing five groups within the MRC HTMR Network; the UKCRC Registered CTU Network; the UK Trial Managers' Network; The Global Health Network; Health Research Board Trials Methodology Research Network in Ireland; Health Data Research (HDR) UK; and additional groups from 25 UK universities with strong trials methodology expertise. Collaboration with industry groups, including large pharma companies and regulatory bodies, will be encouraged.

There remains a strategic need for enhanced coordination, both to avoid losing the momentum within the community, and to develop capacity and capability at the cutting edge of trials expertise to enable the innovative to become the routine. This new multi-stakeholder partnership will allow broader horizon scanning, and an agility to create groups in new areas as needed. The members have agreed to work in partnership to: add value to each other's programmes; identify new areas for research; strengthen links between trials methodology researchers and trial funders; increase system efficiency by providing a clear route for stakeholder engagement; be the centre of gravity for this area of activity; establish a model for sustainability.

TMRP will continue and further develop successful HTMR Network activities, including the International Clinical Trials Methodology Conference series, Guidance Pack, and automating screening for systematic reviews of trials methodology. Eight Working Groups will focus on key areas: Stratified Medicine, Health Informatics, Global Health, Adaptive Designs, Outcomes, Trial Conduct, Health Economics, and Statistical Analysis. Each Working Group will bring together the experts in the partnership, already working on high-quality scientific programmes, to discuss and focus on a small number of particular areas for short periods, before moving on to other topics. This will allow sharing of new approaches that have been developed, experiences of their practical implementation and discussion of how their use could be encouraged more widely. Discussion will naturally lead to refinements and improved implementation, as well as new ideas for the future.

TMRP will increase international collaborations, through new funding opportunities and existing networks such as the Clinical Trials Transformation Initiative, Society for Clinical Trials, European Clinical Research Infrastructure Network, and the Australian Clinical Trials Alliance.

The partners will create a multidisciplinary PhD cohort, covering the disciplines of statistics, informatics, qualitative methods, computer science, clinical medicine, psychology and economics. Support for our students will be a priority since they are the trials methodologists of the future.

The MRC HTMR Network established the UK as a world leader in trials and trials methodology research. The new Trials Methodology Research Partnership will enhance the UK's profile further, by demonstrating the potential of a whole system approach to trials methodology, and by engaging increasing numbers of participants across the world. One of the unique selling points will be the expertise in both undertaking novel research and achieving implementation in practice. This will produce a step change in the dissemination and adoption of efficient methods through the co-involvement of trials methodology researchers and those designing and delivering trials.

Annex 1: MRC HTMR Network-funded PhD Studentships and Training

"*There are a number of additional unique opportunities that the hub provides, these include: internships, webinars, networking events, access to methodology conferences, and frequent communication about recent research and collaborations. In total I believe the value of the MRC HTMR Network substantially compliments that of the support to PhD students by their university.*"
Charlie Harper, Oxford

Recruitment Process

From 2014, one of the main objectives within the renewal of the MRC HTMR Network was to support capacity building in clinical trials methodology. Therefore the Network funded a cohort of PhD students, undertaking specific projects in trials methodology research.

Between 2014-2018, five recruitment rounds were conducted to form the HTMR Network PhD cohort undertaking PhD projects spanning the full spectrum of trials methodology themes.

For each round the MRC HTMR Network Executive Directors, together with invited experts, reviewed PhD project applications submitted from each of the Hubs. The list of projects was reviewed and refreshed between each round for strategic relevance and feasibility.

Candidates were also invited to submit their own PhD proposals.

To attract the highest possible calibre of candidate, the MRC HTMR Network PhD studentship projects were widely advertised via HTMR Network communications, BMJ, New Scientist, websites (FindAPhD, JOBS.AC.UK) and through various stakeholders and University Masters Course administrators in appropriate subjects. Pre-application discussion with project supervisors was recommended to applicants.

The HTMR Network Executive Committee members scored each application on a 3 point system to determine for those suitable for interview; candidates who met the standard required were invited for interview. Candidates were asked to give a short talk on their research plans (no more than 4 minutes) and the interviews used a core list of questions, together with any appropriate project-specific questions.

The majority of appointed non-clinical HTMR PhD students held a masters degree in a relevant discipline.

A summary of the five recruitment rounds can be found in Table 4, including the number of applications received, PhD candidates interviewed, PhD studentship offers made and accepted.

In total, twenty-three PhD candidates were awarded studentship funding awards from the MRC HTMR Network. This included four clinical research doctoral fellowships and one tuition fees only award. Three individuals withdrew prior to completion due to ill health or to pursue an alternative career path.

Table 4 Summary of recruitment cycles of HTMR Network PhD students

Intake year	Number of projects advertised	Total number of applicants	Invited for interview	Number of offers made	Number of offers accepted
2014	16	60 (32 female, 3 clinical)	19 (12 female, 1 clinical)	6 (5 female, 1 clinical)	5 (4 female, 1 clinical)
2015a	34[16] (7 All Ireland projects removed)	52 (31 female, 5 clinical)	24 (18 female, 4 clinical)	10 (7 female, 1 clinical)	8 (7 female, 1 clinical)
2015b	27	21 (14 female, 3 clinical)	12 (7 female, 3 clinical)	5 (3 female, 1 clinical)	4 (2 female, 1 clinical)
2016	25	14 (6 female, 1 clinical)	9 (6 female, 1 clinical)	7 (6 female, 1 clinical)	6 (5 female, 1 clinical)
2018	10	1 (1 female, 0 clinical)	1 (1 female, 0 clinical)	0	0

Current status of HTMR Network PhD Cohort

At the time of publication, ten HTMR Network PhD studentships have been fully completed on schedule. Table 5 summarises the completed and ongoing PhD studentships as at September 2020.

[16] *Proposals submitted by the ALL-IRELAND hub were only included in the 2014 round, projects submitted in 2015 were withdrawn soon after advertising as the ALL-IRELAND hub funding was withdrawn.*

Table 5 Summary of HTMR Network PhD studentships at August 2020
* Denotes inclusion of extension award due to the impact of COVID-19

Name	PhD title	Institute	Topic	Notes	Date of submission	Time to submission
Jennifer Thompson	Statistical design and analysis of cluster-randomised stepped wedge / phased implementation trials	LSHTM	Trial Design	Four year award	Sept 2017	36 months Awarded
Graham Powell	Using routine data in large multicentre clinical trials	Liverpool	Health Informatics	Clinical fellowship	April 2018	44 months Awarded
Christopher Jarvis	Spatial analysis of cluster-randomised trials	LSHTM	Trial Analysis		April 2018	36 months Awarded
Heather Catt	Cost-effective modelling for benefit-risk assessment	Liverpool	Trial Analysis		Oct 2018	37 months Awarded
Lucy Beasant	Treatment preference in paediatric randomised controlled trials	Bristol	Trial Conduct	Four year award	Dec 2018	50 months Awarded
Gemma Clayton	Incorporating external evidence syntheses in the analysis of a clinical trial	Bristol	Evidence Synthesis		Jan 2019	37 months Awarded
Lydia Emerson	Designing a process evaluation framework for understanding factors that impact on successful delivery of trials investigating complex critical care interventions	Queens University Belfast	Trial Conduct	Four year award	May 2019	54 months Awarded
Danielle Edwards	Exploring the use of routine datasets for recruitment and follow-up in randomised trials	Oxford	Health Informatics		June 2019	44 months Awarded
Daniel Hill-McManus	Development and application of linked pharmacometric-pharmacoeconomic analyses in clinical drug development	Bangor	Health Economics		June 2019	41 months Awarded

Name	PhD title	Institute	Topic	Notes	Date of submission	Time to submission
Katherine Fairhurst	Optimising the design and evaluation of pilot work to inform efficient RCTs in surgery.	Bristol	Trial Conduct	Clinical fellowship	Oct 2019	36 months Awarded
Ashma Krishan	The analysis and reporting of time to event data in randomised controlled trials: impact on evidence synthesis and cost effectiveness	Liverpool	Trial Analysis	Part time		Award end date: Oct 2021
Violeta Razanskaite	Record-keeping in patients with inflammatory bowel disease (IBD) within electronic patient record systems	Liverpool	Health Informatics	Clinical fellowship		Award end date: Jan 2021*
Nicola Farrar	Exploring patient perspectives of recruitment in randomised controlled trials	Bristol	Trial Conduct			Award end date: Apr 2021*
Kirsty Garfield	Developing a modular resource-use questionnaire for use in RCTs	Bristol	Health Economics			Award end date: Mar 2021 *
Danielle Johnson	Evidence synthesis for biomarker validity to inform biomarker-stratified trials	Liverpool	Stratified Medicine			Award end date: Feb 2021*
Karen Hughes	Methods to assess and improve the uptake of core outcome sets	Liverpool	Outcomes	Part time		Award end date: July 2021*
Lauren Bell	Design of trials for health related smart phone apps	LSHTM	Health Informatics			Award end date: Dec 2021*
Rachel Maishman	Development of an objective measure of clinical recovery after cardiac surgery for use in RCTs	Bristol	Trial Design	Part time		Award end date: Dec 2021*
Diasmer Panna Bloe	Evaluating electronic data capture systems for the collection of patient reported outcomes and related data	Oxford	Health Informatics	Fees only award		Award end date: Oct 2021*
Charlie Harper	Can routine healthcare data be used to efficiently and reliably follow-up participants in renal trials: analyses using linked data form 2 large renal trials	Oxford	Health Informatics	Part time		Award end date: Oct 2023*

MRC HTMR Network funded PhD Training and Development

In addition to funding PhD studentships, the HTMR Network encouraged annual training for the HTMR Network cohort to add further value to the PhD programme and prepare the students for future careers in trials methodology.

The HTMR Network PhD cohort training was overseen by Louise Bowman, University of Oxford (2014-2017) and Jamie Kirkham, University of Manchester (2017-2019) who held the role of the HTMR Network PhD Student Academic Lead, with support from the HTMR Network Coordinator.

(i) MRC HTMR Network PhD Student Symposia

Since 2011 the MRC HTMR Network has hosted annual training symposia for the students. Five symposia took place during the MRC HTMR Network award (2014-2019), bringing together both the MRC HTMR-funded PhD students and the other hub trials methodology PhD students.

The meetings focussed on skills development, career guidance and talks from trials methodologists about specific topics of potential value to the cohort. There were also opportunities to socialise as a cohort, creating a source of peer support and communication channel to share common experiences and challenges faced during trials methodology doctoral training. The dates, attendance numbers and content of the symposia are summarised in Table 6.

MRC HTMR Network PhD student symposia feedback

"*We have learned about each other's research at the annual HTMR PhD student symposia and these meetings, and evening social events, have provided excellent opportunities to network, sharing experiences and offering support to each other. Given the unique challenges involved in undertaking a PhD, the value of this peer support cannot be understated.*" Heather Catt, Liverpool

"*These [student symposia] events are incredibly useful for PhD students in trials methodology research as they allow us both to broaden our understanding of different areas of research, but also encourage us to hone our own research questions and gain insightful questions from other students.*" Charlie Harper, Oxford

Table 6 An overview of HTMR Network PhD training symposia held between 2014-2018

	Number of PhD attendees		
Date and location	**HTMR Network PhDs**	**Other hub PhDs**	**Activities and topics covered**
5th October 2014 London	5	11	• Introduction to the MRC HTMR Network • Multi-arm, multi-stage trials • Preparing and delivering PhD research presentations • Careers • Trials methodology research at London Hub
17-18th November 2015 (Followed ICTMC 2015) Glasgow	16	6	• Social and networking evening • 'Building Networks' Workshop (Facilitator: Emma Gillaspy, UCLAN) • Quality-by-Design: Tackling errors that matter (Martin Landray, Oxford) • Trial Forge: Improving the efficiency of randomised trials (Shaun Treweek, Aberdeen)
12th October 2016 Birmingham	11	1	• Post-doc talks "If I were starting my PhD now I would…" (Tim Morris, UCL; Marion Mafham, Oxford; Hareth Al Janabi, Birmingham) • Trials and tribulations: building a career in Trials Methodology Research (Sara Brookes, Bristol/Birmingham) • Workshop: Communication and pitching skills for scientists (Facilitator: Caroline van den Brul, British television producer and author of *Essential Communication and Pitching Skills for Scientists*)

	Number of PhD attendees		
Date and location	**HTMR Network PhDs**	**Other hub PhDs**	**Activities and topics covered**
20-21st March 2018 London	13	0	• Social and networking evening • Overview of the HTMR Network • 'Speed-dating' PhD introductions • PhD guidance (Former MRC BSU PhD student, Maxine Bennett) • Discussion of PhD training needs • Writing for publication' workshop (Trish Groves, former BMJ deputy editor and head of research at the BMJ) • Career talks from methodologists in academic and industry research fields (Speakers: Kerry Woolfall, University of Liverpool; Karen Sinclair, Senior Biostatistician Novartis, Basel; Mary Oldham, GSK, UK)
25-26th September 2018 (Followed HTMR Network 2018 Annual Meeting) London	14	0	• Social and networking evening • Applying for a fellowship (Speakers: Sam Rowley, MRC Programme Manager (Methodology); Laura Bonnett, Tenure Track and NIHR Post-Doctoral Fellow, University of Liverpool; Duncan Wilson, MRC Skills Development Fellow, University of Leeds; and Karen Coulman, NIHR/HEE clinical lecturer, Bristol University) • Disseminating PhD research via Social Media (Twitter) and Scholarly Networks (Facilitator: Alastair Horne, British Library and Bath Spa University)

(ii) International Clinical Trials Methodology Conference (ICTMC)

ICTMC meetings were organised by the MRC HTMR Network and were held at venues across the UK on alternate years between 2011-2019, during which five conferences were held. In 2017, ICTMC joined with the SCT Annual Meeting bringing together a larger number of trialists and trials methodologists from all over the world.

MRC HTMR Network PhD students received complimentary registration to ICTMC meetings as part of their PhD award. ICTMC was an ideal opportunity to present PhD research and also network with MRC HTMR Network colleagues as well as with trials methodologists from all over the world.

A PhD social and networking event was held during each ICTMC meeting bringing together the MRC Network HTMR PhD cohort, hub PhD students and, in 2019, the HRB-TMRN and TMRP PhD cohorts. These social events also offered an opportunity for members of the cohort to meet MRC HTMR Network directors and working group co-leads.

An ICTMC education programme was also available to PhD students in 2019 to access specialist training in all disciplines of trials methodology.

Table 7 illustrates the growth in attendance (including number of countries represented) and the attendance numbers of MRC HTMR Network PhD students attending and presenting at the 2015, 2017 and 2019 meetings. * Note 2015 had the highest number of HTMR Network PhD student attendees as it reflects when the highest number of HTMR PhD were actively registered prior to thesis submissions, sickness absences, maternity absences and withdrawals which impacted numbers in later meetings.

Table 7 ICTMC 2015-2019 delegate information

ICTMC date and location	Total number of delegates	Number of countries represented	Number of active HTMR PhD students attending	Number of HTMR PhD students presenting
November 2015, Glasgow	638	8	17*	7 Poster 4 Oral
May 2017, Liverpool	1060	27	13	11 Poster 2 Oral
October 2019, Brighton	738	16	12	5 Poster 5 Oral

Training Needs Survey and Feedback

During autumn 2017 a training needs survey was issued to the HTMR PhD student cohort to begin identifying themes to be included in future HTMR Student symposia. Feedback was also collated after each symposium.

Common themes which emerged included ‘Academic writing’, ‘Careers within and outside trials methodology’, ‘Applying for fellowships’ and ‘Using Social Media to disseminate PhD research’. These themes were addressed in the 2018 symposia programmes, together with overviews of the HTMR Network as requested by PhD students who joined the cohort in 2017.

In the feedback the PhD cohort reconfirmed the importance of socialising with other trials methodology PhD students as part of the training programme as a source of peer support and an

opportunity to share experiences. Students were also keen to understand how they could maximise their time during the PhD gaining experience in activities which would be of benefit to future careers.

(iii) Observer attendance at the Annual BMJ Statistical Editors' meeting

Between 2017-2018, three students accompanied Jamie Kirkham as observers to the Annual BMJ Statistical Editors' Meetings which were held in London each December. The MRC HTMR Network supported travel expenses to the meeting.

"I had the opportunity to attend the BMJ annual editor's meetings which is only open to BMJ editors and BMJ statisticians; I observed how they decided which papers would go on to be published. This was a great opportunity to see what the BMJ looks for in papers they want to publish, and to meet the late Doug Altman." Gemma Clayton, Bristol

HTMR Network PhD students were also encouraged to join the HTMR Network Working groups.

(iv) MRC HTMR Network PhD Internships

The HTMR Network has funded internships involving visits to partners in industry and institutions with specialist centres, offering valuable supplementary experience and training.

Gemma Clayton – Novartis
In 2017 Gemma Clayton, University of Bristol, completed a 12 week internship with Novartis, Switzerland. This internship was fully funded by Novartis. Here is an account from Gemma about her experience which contributed to her PhD thesis and produced a first authored publication.

"I had the opportunity to do an internship at Novartis, in Basel for 3 months from July - September last year (2017). This involved working on a methodological project which was closely related to my PhD (about making more use of existing data to inform a new trial).I was anxious about going to do something new and living in a new country; but equally did not want to pass up the opportunity to work within a pharmaceutical company and obviously live in Switzerland. And it was the best experience in my career so far!

I got to work closely with clinical colleagues which meant being able to convey statistical knowledge in a way which was understood. Apart from learning new skills (I learnt to program in R which is something I couldn't do before I went), I also got the chance to explore Switzerland which was incredible. My work life balance at Novartis was definitely better than it is now and was very much a welcome break from my PhD!"

Daniel Hill McManus – Pfizer
In 2018 Daniel Hill McManus, Bangor University, completed a 12 week Internship with Pfizer. The MRC HTMR Network funded stipend payments during the internship as well as travel and accommodation costs. The internship not only contributed to Daniel's thesis but has also led to a publication.

"*During the final year of my MRC Network of Hubs for Trials Methodology Research studentship I spent three months within Pfizer's Global Pharmacometrics group at their site in Sandwich, Kent. During this time, I had the opportunity to conduct some analyses of data from a clinical trial of an active developmental compound. Supported by both the MRC and Pfizer, I also spent a week visiting some Pfizer R&D sites on the east coast of the US. The greatest benefit to me from this experience were the insights it provided regarding the workings of the pharmaceutical industry and*

the way in which drug development projects are managed. This was especially valuable in the construction of my thesis and journal publications, since the methodology that was the focus of my research is applicable within drug development. The collaboration with Pfizer's Pharmacometrics group has continued beyond my PhD studentship and we have recently submitted a further manuscript for publication."

Nicola Farrar – QUEST Centre
In 2019 Nicola Farrar, University of Bristol, was awarded travel funding to support study visits to the Qualitative Research in Trials Centre (QUEST) in Galway, Ireland. Nicola is due to make a further visit to QUEST during 2020. Here is a brief account from Nicola of what has been achieved to date.

"*During Spring 2019 I was able to spend some time at NUI Galway thanks to a MRC HTMR Network Internship I was awarded to undertake a qualitative evidence synthesis in collaboration with the QUEST team. Whilst in Galway I received a great deal of feedback and support for the development of my synthesis, in particular help with the search strategy and sampling techniques. It was so valuable to spend time with a group with so much experience undertaking evidence syntheses, and to build the connections for when I returned home. Since my visit, I've continued to work on my evidence synthesis alongside my primary PhD data collection, and am currently in the process of submitting the protocol paper for publication. The synthesis will form a key part of my thesis, and brings a new angle to my research.*"

Danielle Johnson – University of Manitoba
In 2019, Danielle Johnson was awarded funding from the UKRI UK-Canada Globalink Doctoral Exchange Scheme to undertake a project addressing the question: 'Is there sufficient evidence to support the inclusion of genetic variants in antipsychotic pharmacogenetic tests?' Danielle will visit the University of Manitoba, Canada, in 2021.

Post-PhD employment and destination

Eleven MRC HTMR Network PhD awardees have successfully gained employment in academic research or clinical research which are closely related or affiliated to trials methodology research. Post PhD employment has been secured in academic fields in statistics, trial management and also wider disciplines including public health, epidemiology, health economics and surgical trials. Both clinical and non-clinical students noted benefits for their career from being in the cohort:

"*The MRC HTMR Network student symposia have offered training on generic research skills …… They have helped me to write two papers, one of which was published earlier in 2019. They have also helped me to communicate my research effectively and develop a research proposal for a clinical lectureship at the University of Manchester. I am pleased to report that I started the post in November 2018.*" Heather Catt, Liverpool

"*The PhD events themselves have also been very helpful with preparing us for not just successfully completing the PhDs but also for our lives post PhD too. I feel everything I learnt over the past 4-5 years has allowed me to progress my career."* Ashma Krishan, Liverpool

Table 8 depicts the types of roles and employment secured by HTMR Network PhD graduates after completing their PhD studies. All have been successful in gaining employment relevant to their PhD studentship.

Table 8 Post-PhD destinations of HTMR Network PhD graduates

Name	PhD host institution	Date of submission	Date of starting role	Post PhD role / destination	Research Discipline
Danielle Edwards	Oxford	Jun 2019	Oct 2018	Research Associate in Medical Statistics and Epidemiology, CF EpiNet group, Imperial University	Medical statistics, informatics, trial methodology
			April 2020	Research Fellow at the department of Biostatistics and Health Informatics at King's College London	
Jennifer Thompson	LSHTM	Sept 2017	October 2017	Research Associate, Trial Statistician, LSHTM	Statistics
			August 2019	Assistant Professor, Trial Statistician, LSHTM	
Lydia Emerson	Belfast	May 2019	October 2018	Research Fellow, City University of London	Process evaluation of complex intervention trials
Lucy Beasant	Bristol	Dec 2018	Jan 2019	Senior Research Associate, University of Bristol	Qualitative research
Gemma Clayton	Bristol	Jan 2019	Jan 2019	Senior Research Associate, MRC Integrative Epidemiology Unit (IEU), University of Bristol	Biostatistics, Epidemiology
Christopher Jarvis	LSHTM	April 2018	May 2018	Research Fellow, LSHTM	Biostatistics
Graham Powell	Liverpool	April 2018	October 2018	Neurology SpR training, Liverpool	Clinical Neurology, electronic health data
Heather Catt	Liverpool	Oct 2018	Nov 2018	Clinical Lecturer in Public Health, Public Health Registrar. University of Manchester	Public Health. Trial outcomes
Katherine Fairhurst	Bristol	Oct 2019	Oct 2019	SpR training, University of Bristol	Surgical trials
			June 2020	Academic Clinical Lectureship, University of Bristol	
Daniel Hill McManus	Bangor	June 2019	Feb 2019	Research Fellow in Pharmacoeconomics, University of Bangor	Health Economics
Ashma Krishan	Liverpool	Thesis pending	Oct 2019	Research Associate, University of Manchester	Statistics

HTMR Network PhD publications

Many of the HTMR PhD cohort have successfully published their PhD research in peer reviewed journals, with more publications expected to follow as current HTMR PhD students complete their research. Research articles published to date are listed in Appendix 1 of the main report document.

Appendices

Appendix 1: MRC HTMR Network publications 2014-2019
Appendix 2: Citation analysis for MRC HTMR Network publications 2014-2020
Appendix 3: MRC HTMR Network-funded projects 2014-2019
Appendix 4: MRC HTMR Network impact project funding awarded 2018-2019
Appendix 5: MRC HTMR Network Guidance Pack
Appendix 6: MRC HTMR Network leveraged funding 2009-2019
Appendix 7: HTMR Network Response to the MRC mid-term report feedback

Appendix 1:

MRC HTMR Network publications 2014-2020

Adaptive Designs

Pushpakom SP, Taylor C, Kolamunnage-Dona R, et al. Telmisartan and Insulin Resistance in HIV (TAILoR): protocol for a dose-ranging phase II randomised open-labelled trial of telmisartan as a strategy for the reduction of insulin resistance in HIV-positive individuals on combination antiretroviral therapy. *BMJ Open*. 2015 15;5(10):e009566. doi: 10.1136/bmjopen-2015-009566

Wason J, Magirr D, Law M, Jaki T. Some recommendations for multi-arm multi-stage trials. *Stat Methods Med Res*. 2016;25(2):716-727. doi:10.1177/0962280212465498

Jansen JO, Pallmann P, MacLennan G, Campbell MK; UK-REBOA Trial Investigators. Bayesian clinical trial designs: Another option for trauma trials? *J Trauma Acute Care Surg*. 2017; 83(4):736-741. doi:10.1097/TA.0000000000001638

Avery KN, Williamson PR, Gamble C, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open*. 2017;7(2):e013537. doi:10.1136/bmjopen-2016-013537

Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16(1):29. doi:10.1186/s12916-018-1017-7

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Appendix 2:
Citation analysis for MRC HTMR Network publications 2014-2020

Figure 1 Cumulative citations for papers published 2014-2020 over time

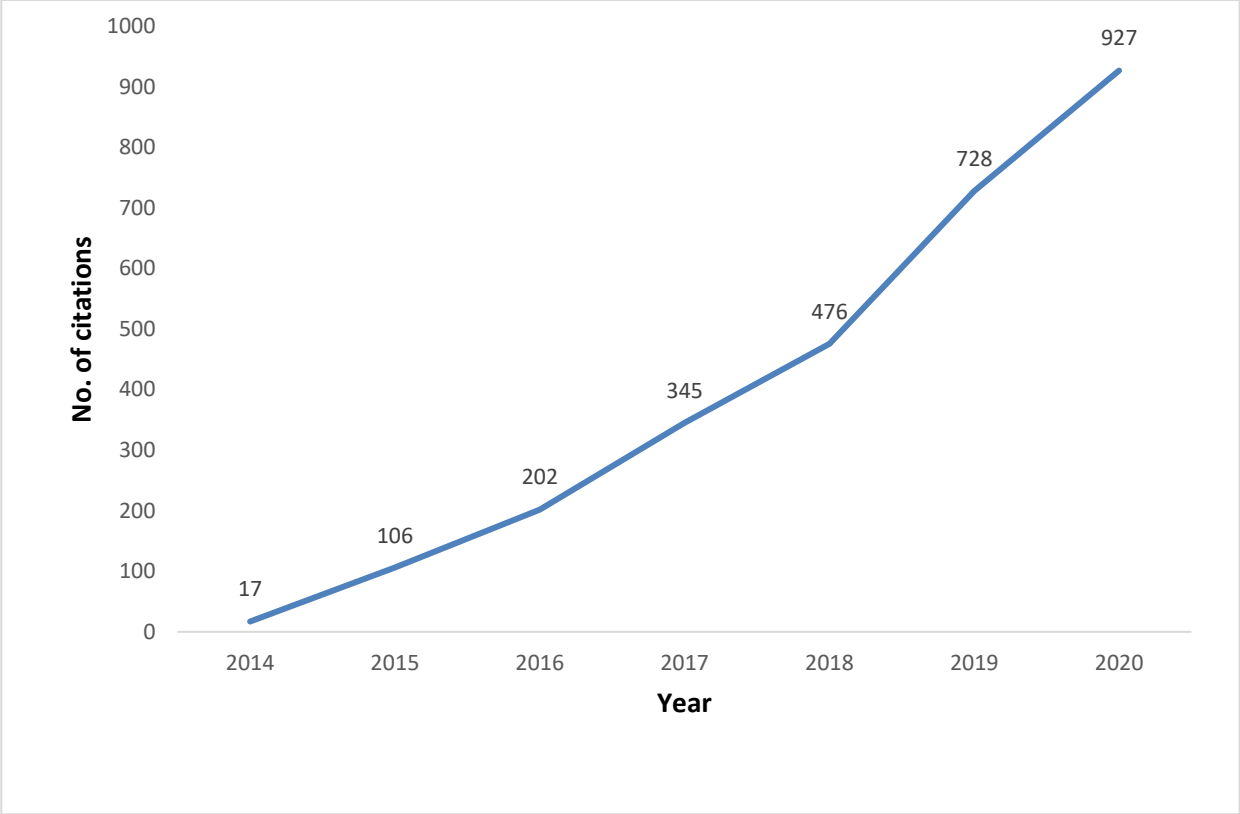
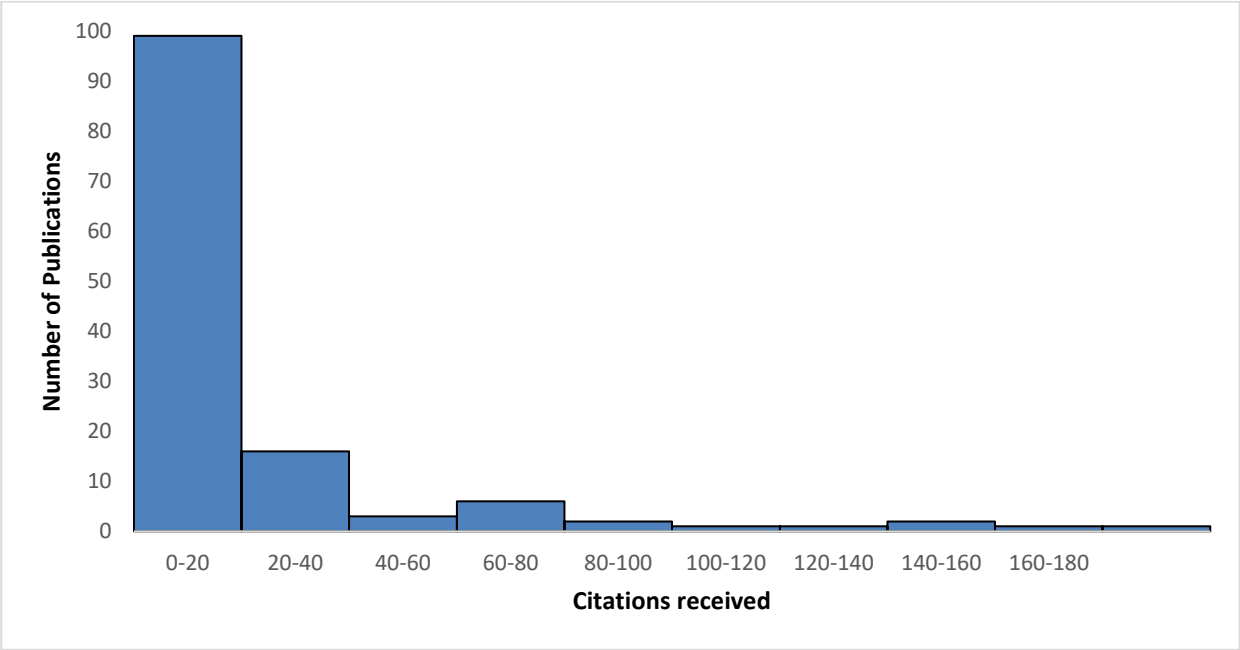


Figure 2 Distribution of total citation number for articles published 2014-2020



Appendix 3:

MRC HTMR Network-funded projects 2014-2019

ID	Host university	Lead applicant	Title
N55	University of Liverpool	Paula Williamson	Development of a quality assessment tool for core outcome set development
N57	University of Bristol	Joanna Thorn	Identification of items for inclusion in a standardised resource-use measure
N61	University of Bristol	Jelena Savovic	Refinement of and extension to the Cochrane Risk of Bias tool for Randomised trials
N62	University of Liverpool	Kerry Woolfall	Methods for Patient and Public Involvement (PPI) in Clinical Trials: A Research Priority and Agenda Setting Exercise
N64	University of Manchester	Peter Bower	Studies Within a Trial and Embedded Trials: Current barriers and facilitators to implementation in funders and clinical trials units
N65	University of Bristol	Joanna Thorn	Mapping current usage of Health Economic Analysis Plans (HEAPs)
N66	University of Oxford	Richard Bulbulia	Developing a patient and public involvement intervention to enhance recruitment and retention in surgical trials
N67	University of Liverpool	Jamie Kirkham	Development of an interactive website for outcome reporting bias research
N68	University of Lancaster	Lisa Hampson	Clinical trials in small populations: methodological challenges and solutions: A workshop
N73	University of Manchester	Peter Bower	Exploring design and use of incentives for recruitment and retention in clinical trials: A workshop and a review
N76	University of Liverpool	Andrea Jorgensen	Online tool for guidance on designing biomarker-guided randomised controlled trials
N78	University of Lancaster	Thomas Jaki	Development of user-friendly web-based software for conducting Bayesian Phase I dose-escalation studies
N79	University of Bristol	Howard Thom	Efficient sample schemes for estimation of value of information of future research

ID	Host university	Lead applicant	Title
N83	University of Lancaster	Tom Palmer	Improving the design and analysis of trials for efficacy and mechanisms evaluation: workshop and training days.
N84	University of Liverpool	Paula Williamson	What might a Global Health Trials Methodology Research Agenda look like?
N85	University of Bristol	Jane Blazeby	Guidance to optimise pilot study design and conduct: A joint HTMR and NIHR HTA 'Research on Research' proposal
N86	University of Bristol	Athene Lane	Developing a medical work force to design and conduct trials to improve evidence-based practice: a case study of surgical Trainee Research Collaboratives and a stakeholder workshop
N87	University of Bristol	Alicia O'Cathain	Advancing the integration of mixed methods in clinical trials: a two day summit
N89	University of Liverpool	Andrea Jorgensen	Improving the efficiency of biomarker-guided trial designs by using continuous biomarker information
N90	University of Cambridge	James Wason	Developing CONSORT guidance for adaptive clinical trials
N91	University of Bristol	Joanna Thorn	Health Economics Analysis Plans: developing content guidance through consensus
N96	LSHTM	Elizabeth Williamson	Covariate adjustment in randomised trials
N97	University of Cambridge	Michael Grayling	Investigating the reasoning behind the use of non-randomised single-arm designs in phase II clinical trials
N100	University of Bristol	Robert Hinchliffe	Improving the evaluation of medical devices with development of a generic core outcome set (COS): a key stakeholder workshop
N101	University of Liverpool	Carrol Gamble	Extending ORRCA to create a central resource for retention research within clinical trials (ORRCA 2)

Appendix 4:

MRC HTMR Network impact project funding awarded 2018-2019

ID	Host university	Lead applicant	Impact award title and description of impact activity
R1	University of Liverpool	Paula Williamson	COMET • Bursaries enabled four LMIC researchers to attend COMET VII in 2018, which further increased their awareness and understanding of core outcome sets. • COMET's strategy to further support the development, dissemination and use of COS in LMICs was further progressed through a number of follow on activities.
R44	University of Liverpool	Carrol Gamble	Development of Guidance for Statistical Analysis Plans for Clinical Trials • Wide dissemination of a downloadable SAP checklist and elaboration document. • SAP guidance endorsement within the BMJ's publication policy. • Agreement from funders (Wellcome Trust, NIHR) to reference the SAP guidance within their policies.
R53	University of Bristol	Nicola Mills	Developing, delivering and evaluating training courses for recruiters to randomised trials • Workshop materials were refined, updated and refreshed for a broader audience. • Successful workshops were delivered during 2019 in the UK and at international conferences (SCT and ICTMC). • Publication in preparation for submission in late 2020. • Workshops to be held annually by University of Bristol from 2021.
N57	University of Bristol	Joanna Thorn	Identification of items for inclusion in a standardised resource-use measure • The MODRUM questionnaire has been improved with a professional design to facilitate future uptake of the questionnaire by both researchers and patients.

ID	Host university	Lead applicant	Impact award title and description of impact activity
N61	University of Bristol	Jelena Savovic	Refinement of and extension to the Cochrane Risk of Bias (RoB 2) tool for randomised trials • The RoB 2 tool was further piloted, refined and published (Sterne et al., 2019). • Wide dissemination of the RoB 2 tool via workshops, lectures and webinars. • An ongoing pilot of the implementation of RoB 2 is currently being undertaken by Cochrane, the process of which will be published as an editorial in autumn 2020.
N83	University of Lancaster	Tom Palmer	Improving the design and analysis of trials for efficacy and mechanisms evaluation: training days • A training day was successfully delivered in May 2019 with 22 attendees.
N86	University of Bristol	Athene Lane	Developing a medical work force to design and conduct trials to improve evidence-based practice: a case study of surgical Trainee Research Collaboratives (TRC) • An animated 'digital story' describing the top five strategies for engaging surgeons in trials is available on You Tube and has been viewed over 325 times. • The 'digital story' has been disseminated via stakeholders, Trainee Research Collaboratives and to ICTMC 2019 attendees.
N91	University of Bristol	Joanna Thorn	Health Economics Analysis Plans (HEAP): developing content guidance through consensus • Successful delivery of two 'hands-on' training workshops to guide health economists in writing analysis plans for economic evaluations (at Bristol and ICTMC 2019). • A publication describing HEAPs will be published autumn 2020.

ID	Host university	Lead applicant	Impact award title and description of impact activity
N103	University of Liverpool	Susie Dodd	Evaluation of digital health interventions (DHI): a workshop and "Issues to consider" document • A DHI evaluation workshop was held December 2019 with 35 attendees. • The discussions and knowledge exchange during the workshop are to be summarised in an “Issues to consider” document. Submission date: November 2020.
N104	University Manchester	Peter Bower	Building on success: a workshop to synthesise learning on patient and public involvement from a portfolio of MRC Hub projects • A workshop brought together patients and trial methodologists in November 2019 to initiate compilation of examples and develop guidance for effective Patient, Public Involvement & Engagement (PPIE) in the context of Trial Methodology Research. • A detailed workshop report, which includes a summary of the common themes and issues which were identified, has been disseminated online and across TMRP.
N105	MRC CTU at UCL	Sharon Love	Practicalities in running trials with more than one primary hypothesis and an adaptive element (Platform trials) • A research publication titled: ‘Running a trial with more than one primary hypothesis and an adaptive element’, has been drafted and edited for submission autumn 2020.

Appendix 5:

MRC HTMR Network Guidance Pack (as at August 2020)

Guidance pack

COMET: Core Outcome Measures in Effectiveness Trials

DIRUM: Database of Instruments for Resource Use Measurement

CONSORT PRO: Patient-Reported Outcomes

ACE: Adaptive designs CONSORT Extension

Monitoring trials efficiently: The role of central statistical monitoring

Sharing participant data:Good practice principles for sharing individual participant data from publicly funded clinical trials

CONNECT: Consent methods in paediatric emergency and urgent care trials

MAMS: Some recommendations for multi-arm multi-stage trials

Qualitative research: Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers

Surgical trials: Interventions in randomised controlled trials in surgery: issues to consider during trial design

PIRRIST: Patient and public Involvement to enhance Recruitment and Retention In Surgical Trials

SWATs:Online database for Studies Within A Trial (SWAT) and Studies Within A Review (SWAR)

Doing trials within trials A qualitative study of stakeholder views on barriers and facilitators to the routine adoption of methodology research in clinical trials

Rheumatoid Arthritis: Consensus Decision Models for Biologics in Rheumatoid and Psoriatic Arthritis: Recommendations of a Multidisciplinary Working Party

Trial Steering Committees: Exploring the role and function of trial steering committees: results of an expert panel meeting.

Why not to use A+B design: A discussion of appropriate design for phase I dose escalation studies.

Optimising Recruitment: the Quintet Recruitment Intervention

COS-STAR, COS-STAD and COS-STAP: Core Outcome Set-STAndards for Reporting, Core Outcome Set-STAndards for Development and Core Outcome Set - STAndardised Protocol items

RoB 2.0: Revised Cochrane Risk of Bias tool 2.0 for randomised trials.

ORBIT: Outcome Reporting Bias in Trials

ORRCA: Online Resource for Recruitment Research in Clinical TriAls

SOS: Search for Oversight Statisticians

SAPs: Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

BiGTeD: Biomarker-guided trial designs

Internal pilot studies: developing progression criteria

Pilot and feasibility studies: when to do an internal or external pilot

MODEsT Software: (MOdel-based Dose-Escalation Trials)

ISRUM: Core Items for a Standardised Resource Use Measure

Phase II Oncology Trials: Considerations and recommendations on using randomised designs

Appendix 6:

MRC HTMR Network leveraged funding 2009-2019

(related to HTMR Network projects or advice provided by HTMR members)

Trial design					
HTMR lead(s)	**CI (if different)**	**Value of award**	**Award / Trial title**	**Funder**	**Brief overview of HTMR Network input**
Jane Blazeby (Bristol) Bridget Young (Liverpool)	Nigel Hall (Southampton)	£482,882	CONTRACT: CONservative TReatment of Appendicitis in Children Trial - feasibility study	NIHR HTA	HTMR Network award project findings (Lead: Young) informed study
Jane Blazeby (Bristol)	Amber Young (Bristol)	£133,929	Core Outcomes for Burn Care Research: short-term outcomes and outcome measures for use in burn care efficacy trials.	Scar Free Foundation	Developed in relation to a HTMR Network funded research project (COMET)
Gráinne Gorman (Newcastle)		£2,067,305	AIMM (Acipimox in Patients with Mitochondrial Myopathy)	MRC (BMC:DPFS)	Outreach Officer (Pallmann) advised on the trial
Robin Grant (Edinburgh)		£1,554,047	SPRING - Seizure Prophylaxis IN Glioma	NIHR HTA	Outreach Officer (Pallmann) advised on the trial HTMR Network members are Co-Is
Will Hollingworth / Jo Thorn (Bristol)		£59,016	PECUNIA: ProgrammE in Costing, resource use measurement and outcome valuation for Use in multi-sectoral National and International health economic evaluAtions	EU Horizon 2020	HTMR Network award project findings (Lead: Thorn) informed study
Dyfrig Hughes (Bangor)	Steven Julious (Sheffield)	£49,853	Benefit-Risk Assessment to Inform Non-Inferiority and Superiority study design	MRC-NIHR	Developed following a HTMR Network funded research project
Thomas Jaki (Lancaster)		£443,152	Designing & analysing multi-arm multi-stage clinical trials with one or more endpoints	MRC	Developed following a HTMR Network funded research project

Trial design					
HTMR lead(s)	**CI (if different)**	**Value of award**	**Award / Trial title**	**Funder**	**Brief overview of HTMR Network input**
Jan Jansen, Marion Campbell (Aberdeen)		£1,302,124	REBOA: Resuscitative Endovascular Balloon Occlusion of the Aorta	NIHR HTA	Outreach Officer (Pallmann) advised on the trial
Mark McGurk (UCL)		£1,033,008	LOOC: Lymphatic mapping Of Oropharyngeal Cancer	NIHR EME	Direct impact of HTMR Network funded workshop (Lead: Shaw) on developing the trial
Clare Pain (Liverpool)		£535,259	MYPAN: Mycophenolate mofetil for polyarteritis nodosa	AR UK	Outreach Officer (Pallmann) and Adaptive Designs Working Group advised on the trial Co-Is include HTMR Network members
Munir Pirmohamed (Liverpool)		£892,361	TAILoR: TelmisArtan and InsuLin Resistance in HIV	NIHR EME	HTMR Network Adaptive Designs Working Group advised on MAMS trial design
Howard Thom (Bristol)		£510,646	What is the value of adaptive designs? Estimating expected value of sample information for adaptive trial designs	MRC New Investigator Research Grant	Developed following a HTMR Network funded research project
James Wason (MRC BSU/Newcastle)		£226,204	Developing efficient perpetual platform trials to study multiple treatments and multiple biomarkers	MRC MRP	Developed in conjunction with HTMR Network working group
James Wason (MRC BSU/Newcastle)		£55,629	Costing Adaptive Trials (CAT) Developing best practice for CTUs supporting adaptive trials	MRC	Developed in conjunction with HTMR Network working group
James Wason (MRC BSU/Newcastle)	David Russell (Leeds)	£1,787,716	MIDFUT: Multiple Interventions of Diabetic Foot Ulcer Treatment Trial	NIHR HTA	HTMR Network Adaptive Designs Working Group advised on MAMS trial design

Trial design					
HTMR lead(s)	**CI (if different)**	**Value of award**	**Award / Trial title**	**Funder**	**Brief overview of HTMR Network input**
Paula Williamson (Liverpool)		£720,000	COMET Initiative / Senior Investigator award	NIHR	Follow-on funding to continue a HTMR Network funded research project
Paula Williamson (Liverpool)		€14.5m (€220,000 to Liverpool)	CORBEL (Coordinating Research Infrastructures Building Enduring Life-science services	European Commission	Developed following a HTMR Network funded research project (COMET)
Paula Williamson (Liverpool)		€3,864,090	Innovative Training Network: MIROR (Methods in Research on Research)	European Commission	Developed in relation to a HTMR Network funded research project (COMET)
Paula Williamson (Liverpool)	John Keady (Manchester)	£2,000,000	Neighbourhood and Dementia: a mixed methods study'	ESRC/NIHR	Developed in relation to a HTMR Network funded research project (COMET)
Paula Williamson (Liverpool)		£229,405	Core outcome set for anal cancer studies	NIHR RfPB	Developed in relation to a HTMR Network funded research project (COMET)
Paula Williamson (Liverpool)		£1,125,047	Changing Agendas on Sleep, Treatment and Learning in Childhood Epilepsy (CASTLE)	NIHR PGfAR	Developed in relation to a HTMR Network funded research project (COMET)
Paula Williamson (Liverpool)		£66,000	Determining core outcome measures in MPS II	Shire Pharmaceuticals Educational Grant	Developed in relation to a HTMR Network funded research project (COMET)
Paula Williamson (Liverpool)		£87,570	Core Outcome Set for intervention trials in Postpartum Haemorrhage	British Medical Association	Developed in relation to a HTMR Network funded research project (COMET)

Trial conduct					
HTMR lead	**CI (if different)**	**Value of award**	**Award / Trial title**	**Funder**	**Brief overview of HTMR Network input**
Peter Bower (Manchester)		£149,827	Patient-centred trials: developing measures to improve the experience of people taking part in clinical trials	NIHR RFPB	Developed following a HTMR Network funded research project
Peter Bower (Manchester)	David Torgerson (York)	£436,614	Routinely embedding recruitment and retention interventions with randomised controlled trials	MRC MRP	Developed following a HTMR Network funded research project
Carrol Gamble (Liverpool)		£216,175	Losing the losses: understanding the reasons for attrition in randomised trials and developing the evidence to prevent it	MRC MRP	Developed following a HTMR Network funded research project
Carrol Gamble (Liverpool)		£30,000	Continuation funding for ORRCA (Online Resource for Recruitment (and Retention) Research in Clinical TriAls)	HRB-TMRN	Follow-on funding to continue a HTMR Network funded research project
Peter Knapp (York)		£575,953	TRECA study: TRials Engagement in Children and Adolescents	NIHR HS&D	HTMR Network award project findings (Lead: Young) informed study
Athene Lane (Bristol)		£14,536	How to run a good Trial Steering Committee: an online workshop for TSC Chairs of new trials	NIHR CTU Support Funding – Supporting efficient / innovative delivery of NIHR research	HTMR Network award project findings (Lead: Gamble) informed award

Other					
HTMR lead	**CI (if different)**	**Value of award**	**Award / Trial title**	**Funder**	**Brief overview of HTMR Network input**
	Claire Planner (Manchester)	£135,000	Launching Fellowship in Primary Care	NIHR School for Primary care Research	Developed following a HTMR Network funded research project
Jane Blazeby (Bristol)	John Iredale (Bristol)	£20,858,545 (£4.5m: Surgical innovation theme)	NIHR Bristol Biomedical Research Centre	NIHR	
Paula Williamson (Liverpool)		£466,568	Trials Methodology Research Partnership	MRC MRP	Follow-on funding to continue the HTMR Network together with five additional Partner organisations

Appendix 7:

HTMR Network response to the MRC mid-term report feedback

Following the mid-term report feedback provided by the MRP in November 2016 there was only limited time available to make a significant difference during the remaining period of the MRC HTMR Network award. However all points made by the panel were taken on board and actions put in place which allowed them to be addressed in the successful MRC-NIHR Trials Methodology Research Partnership award which began in June 2019. Below are some specific responses to the feedback.

1. Poor history of engagement with industry

Adaptive designs was recognised to be an area of interest to both HTMR and the pharmaceutical industry in particular. A HTMR Network meeting was held in September 2014 with representatives of TransCelerate BioPharma Ltd, an organisation which fosters collaborations with the biopharmaceutical research and development community. The parties summarised their research activities, highlighted relevant projects and collaborators and agreed to communicate regularly.

In 2019 the Adaptive Designs Outreach Officer visited Roche, AstraZeneca and PhaStar with another member of the Adaptive Designs Working Group, with follow-up discussions on technical aspects and potential joint research. To further increase engagement with industry, an Association of the British Pharmaceutical Industry (ABPI) representative was invited to join the TMRP Executive Committee (see section 5).

2. Insufficient consideration of the impact and possibilities of electronic health records and health informatics on trial methodology

Six HTMR Network PhD studentships have focused on the area of electronic health records and health informatics. These are listed in Table 9 below.

Table 9 Summary of the HTMR Network PhD studentships within the theme of health informatics

Institution	Name	PhD title	Status
Liverpool	Graham Powell	An assessment of the use of routinely recorded data in the UK in a randomised controlled trial	Awarded
Oxford	Danielle Edwards	Exploring the use of routine datasets for recruitment and follow-up in large randomised trials	Awarded
Liverpool	Violeta Razanskaite	Record-keeping in patients with inflammatory bowel disease (IBD) within electronic patient record systems	Ongoing
LSHTM	Lauren Bell	Design of trials for health related smart phone apps	Ongoing
Oxford	Diasmer Bloe	Evaluating electronic data capture systems for the collection of patient reported outcomes and related data	Ongoing
Oxford	Charlie Harper	Can routine healthcare data be used to efficiently and reliably follow-up participants in renal trials?	Ongoing

The MRC HTMR Network began to engage with Health Data Research UK (HDR UK) from the formation of the latter in 2018 including inviting HDR UK to MRC HTMR Network events and arranging an organised session with HDR UK at ICTMC 2019.

In December 2019, a MRC HTMR Network Impact award supported a workshop discussing Digital Health Interventions with a "Future issues to consider" publication due to be submitted by the end of 2020.

The MRC HTMR Network Health Informatics Working Group was also active between 2014-2019 and established the strategy for the TMRP Health Informatics Working Group (see section 5).

3. **Consider relevance of stratified medicine and biomarker-driven trials - as central component of the Network's activity and of any future beyond the current funding period**

MRC HTMR Network project and impact funding awards supported the BiGTeD project, where a comprehensive review of over 200 papers of biomarker-guided trial designs was undertaken. The results of the review were published in two separate papers, one focusing on adaptive trial designs and the other on non-adaptive trial designs, and development of a user friendly website (http://www.bigted.org/) which offers a graphical and descriptive written overview of trial designs identified.

In 2017 a MRC HTMR Network PhD was funded, titled 'Evidence synthesis for biomarker validity to inform biomarker-stratified trials'. The MRC HTMR Network Stratified Medicine Working Group was also active between 2014-2019 and established the strategy for the TMRP Stratified Medicine Working Group (see section 5).

4. **Improve expertise and help address methodological challenges in designing, delivering and analysing trials in LMICs**

MRC HTMR Network project funding supported a project titled 'Global Health Trials Methodology Research Agenda' which published identified priorities which could inform a global health trials methodological research agenda. Such an agenda could increase and improve future trials in LMICs and has informed the strategy for the TMRP Global Health Working Group (see section 7).

A MRC HTMR Network Impact Award enabled the COMET Initiative to fund representatives from trials methodology networks in LMICs to attend the COMET VII meeting in 2018 to strengthen connections and increase knowledge in the area of Core Outcome Sets.

Both of these projects were undertaken in collaboration with The Global Health Network, https://tghn.org/ , and this partnership has been strengthened through the TMRP (see section 5).

5. **Varied level of engagement of trials methodologists within and outside hubs**

In 2016 a MRC HTMR Network newsletter and Twitter profile were launched with subscribers steadily growing up to the end of the award. Many subscribers were not originally hub members and were located worldwide. The new TMRP has established a broader trials methodologist community, directly addressing this comment (see section 5).

The continued growth of the biennial ICTMC demonstrates increased engagement with a wider UK and global community beyond the hubs. The 2015 and 2019 conferences attracted >700 delegates. The joint ICTMC 2017 meeting with the Society of Clinical Trials attracted >1000 delegates, including a large proportion of international delegates. In each year held, this was the largest academic led trial on clinical trials methodology. The joint conference with SCT, building on a presentation about HTMR in 2016 at SCT, raised awareness of the work of the MRC HTMR Network across North America and Canada.