Clinical trials strategy

Context

Trials

Randomised controlled clinical trials (hereafter referred to as 'trials') are the most reliable tests of the effects of clinical interventions, forming the basis of changes to guidelines and clinical practice, thereby improving human health. Trials make an important contribution to the impact of the University of Edinburgh's research. In REF 2014, trials underpinned 8/22 (36%) impact case studies submitted to unit of assessment 1 (clinical medicine) and 6/13 (46%) impact case studies submitted to unit of assessment 4 (psychology, psychiatry and neuroscience).

Edinburgh Clinical Trials Unit (ECTU)

ECTU is a UK-CRC registered trials unit based within the Usher Institute at the University of Edinburgh. ECTU provides an infrastructure to design, plan, deliver and report clinical research studies, primarily publicly funded randomised controlled trials. ECTU works closely with the local sponsor, the Academic and Clinical Central Office for Research and Development (ACCORD), which is a partnership between the University of Edinburgh and NHS Lothian. ECTU also has links with the Edinburgh Clinical Research Facility (which is accredited for phase 1 studies), and the University of Edinburgh's Research Support Office. ECTU employs around 63 FTE academic and professional services staff (Jan 2020), including a Director and senior management team (7 staff), a business team (3 staff), a statistics & health economics team (18), a trial management team (25 staff), a data management and programming team (6 staff), a clinical team (7 staff), and quality assurance (1 staff). The wage bill is ~£2.5-£3 million per year. There were 58 active studies on the portfolio at the start of 2020 (~20 were CTIMPs). 90% of ECTU's funding comes from externally won grants and the rest is from NHS Lothian R&D (~£210,000 net per annum).

External review of the clinical trials pathway in Edinburgh

An external panel of NHS R&D Directors and clinical academics with expertise in trials undertook a review of the clinical trials pathway in Edinburgh on 29-30 January 2020. The panel made several recommendations, which have remained under review by a short-life working group including staff from the University of Edinburgh and ACCORD, and which were circulated to clinical academics and other stakeholders in July 2020. Of the recommendations made by the external review, the following are relevant to this strategy for clinical trials (which cross-references these recommendations by their number/letter):

A. *ACCORD and ECTU leadership is strong and will benefit from being empowered through working to a clear over-arching strategy and more senior support.*
B. *Invest in creating the necessary capacity to deliver the agreed strategic plan. This will require investment in:*
    i. *Core funding for ECTU to support grant development for clinical trials*
    ii. *Increased capacity in the ACCORD joint office*
    iii. *A research design service or similar for non-CTIMPs.*
    iv. *Establishing a separate function specifically for global health studies*

C. *In addition, for ECTU:*
   i. *There is an urgent need to take short-term action to address capacity issues. Any further loss of staff presents a high risk that current studies will not be delivered. There is a need to rationalise applications and focus on 'easier wins' such as commissioned calls.*
   ii. *ECTU would benefit from increased clinical input in an advisory form reporting to and supporting the ECTU director.*
   iii. *Transfer ECTU research nurse team to a more appropriate department within the partnership.*
D. *An institutional position on grant applications in relation to prioritisation, peer-review and timelines and support for ECTU and ACCORD in enforcing the position.*
E. *Introduce regular performance monitoring against agreed expectations, which match capacity.*
F. *Develop project management infrastructure, embedded in research teams.*
G. *Reinforce desired culture and behaviours.*

Following the external review, the COVID-19 pandemic caused a rapid relocation of staff supporting trials to domestic workplaces, paused or delayed a large proportion of Edinburgh's ongoing trials, and required methods of recruitment and retention to be redesigned. An additional portfolio of research arose rapidly to address COVID-19. The University of Edinburgh's financial resources declined. However, a short-life working group was convened to consider the recommendations of the external review.

This clinical trials strategy arose from the recommendations of the external review, with reference to the University's current research strategies (see appendix, pp. 10-11) and consultations with key stakeholders (see below, p. 9). This strategy was reviewed on two occasions and approved by the short-life working group.

Clinical trials strategy

This strategy prioritises the purpose and core expertise of a clinical trials unit, which is to develop, design and deliver clinical trials. The structure of this strategy, itemised in the following pages, reflects these three core elements, which are inter-dependent and rely on the capacity and expertise of the clinical trials unit to achieve the aims of the strategy:

Using these three core elements as a framework, the strategy addresses recommendations of the external review of the clinical trials pathway in Edinburgh (see above, pp. 1-2), and includes themes from the University of Edinburgh's research strategies (see appendix, pp. 10-11).

Clinical trials strategy

1. Develop:

Clinical trials

1.1. Clinical trials* led by chief investigators in Edinburgh.
1.2. Clinical trials that will make an impact on human health challenges, at least locally, and preferably globally (appendix), involving any type of intervention (e.g. drug, device, and complex).
1.3. Clinical trials that are informed by sufficient expertise and experience.
1.4. Clinical trials that address the University of Edinburgh's strategic priorities (especially data-driven innovation, digital transformation, global health, and partnership with industry; see appendix, pp. 10-11).
1.5. Clinical trials that synergise with other research strengths of the University of Edinburgh, including experimental/translational medicine, imaging, and data science.
1.6. Funding applications for clinical trials that converge with these scientific priorities (1.2, 1.4 & 1.5), maximise the chances of success (e.g. commissioned research calls), and benefit the business plan (e.g. funders that support the infrastructure of the host institution, such as NIHR/MRC/Wellcome Trust).
1.7. Observational (non-randomised) studies in ECTU *only* when the immediate next step will be a clinical trial (e.g. feasibility studies). Feasibility and pilot studies improve the chances of successful funding and conduct of randomised controlled trials, so external and internal support for them is a priority.
1.8. Methodological research into the design, conduct and analysis of clinical trials.

People

1.9. Capacity to develop and design clinical trials by growing the methodologist workforce to support a Research Design Service.
1.10. Cultures and behaviours that respect and support people conducting clinical trials (e.g. professional services, funding specialists, research governance, methodologists, statisticians, programmers, data managers, trial managers, early career researchers, and chief investigators).
1.11. Equality, diversity, inclusion, expertise and support in all communities of staff supporting and conducting clinical trials.

* The World Health Organization (WHO) defines a clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc."

2. Design:

Clinical trials

2.1. Clinical trials with methodological rigour and low risk of bias, informed by proof of concept, feasibility/pilot data, and patient/carer/public involvement.
2.2. With internal peer review and quality control, wherever possible.
2.3. Clinical trials including methodological innovation and embedded studies into trial methodology where appropriate.
2.4. Processes to develop and deliver clinical trials that are effective, streamlined and tailored to available capacity.
2.5. Clinical trials that are efficient, and economically, environmentally, and socially sustainable.

3. Deliver:

Clinical trials

3.1. Phase 1 clinical trials[†] in the Edinburgh Clinical Research Facility (CRF).
3.2. Phase 2-4 randomised clinical trials[‡] in the Edinburgh Clinical Trials Unit.
3.3. Clinical trials with the highest standards of research integrity.
3.4. Clinical trials with sufficient resource to avoid over-burdening staff.
3.5. Within the staffing capacity in ECTU, ACCORD (e.g. research governance, global health, and pharmacovigilance), and other research facilities.

People

3.6. Education and training for staff supporting the clinical trials pathway in Edinburgh to deliver cutting edge clinical trials (e.g. sharing expertise between funding specialists and R&D staff; networks of trial managers and statisticians; guidance, apprenticeships and mentorship for forthcoming and new chief investigators etc).
3.7. The clinical trials pathway with support from an ECTU clinical advisory group and oversight from a clinical trials strategy committee.

[†] Phase 1 = clinical trials that test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
[‡] Phase 2 = clinical trials that study the biomedical or behavioural intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety. Phase 3 = clinical trials that investigate the efficacy of the biomedical or behavioural intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely. Phase 4 = clinical trials that are conducted after the intervention has been marketed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

Table: Key components of the clinical trials strategy, how they correspond to University strategies or the recommendations of the external review, and suggestions for monitoring concordance with the strategy.

Clinical trials strategy	Relevant strategy (appendix) or review recommendation(s) (pp. 1-2)	Suggested metrics for monitoring
Develop		
1.1. Clinical trials led by chief investigators in Edinburgh	Recommendation D	Proportion of trials led by chief investigators in Edinburgh
1.2. Clinical trials that will make an impact on human health challenges, at least locally, and preferably globally	University of Edinburgh's Strategy 2030; University of Edinburgh's Research Strategy; Usher Institute Strategy 2020-2023	Proportion of trials with global impact
1.3. Clinical trials that are informed by sufficient expertise and experience	Recommendation A; University of Edinburgh's Strategy 2030	Proportion of trial applications where at least one co-applicant has specific expertise and experience in the methodology and disease.
1.4. Clinical trials that address the University of Edinburgh's strategic priorities, especially data-driven innovation, digital transformation, global health, and partnership with industry	Recommendation D; University of Edinburgh's Strategy 2030; University of Edinburgh's Research Strategy; Usher Institute Strategy 2020-2023	Proportion of trials addressing the University of Edinburgh's strategic priorities
1.5. Clinical trials that synergise with other research strengths of the University of Edinburgh	Recommendation D; University of Edinburgh's Strategy 2030; University of Edinburgh's Research Strategy; CMVM 'One Medicine, One Health' strategy; Usher Institute Strategy 2020-2023	Proportion of trials synergising with the University of Edinburgh's strengths

Clinical trials strategy	Relevant strategy (appendix) or review recommendation(s) (pp. 1-2)	Suggested metrics for monitoring
1.6. Funding applications for clinical trials that converge with these scientific priorities, maximise the chances of success, and benefit the business plan	Recommendation C i; Recommendation D	Proportion of funding applications for trials addressing the University of Edinburgh's strategic priorities
1.7. Observational (non-randomised) studies in ECTU *only* when the immediate next step will be a clinical trial (e.g. feasibility studies)	Recommendation D	Proportion of observational studies in the ECTU portfolio that do not lead to a clinical trial as the next step
1.8. Methodological research into the design, conduct and analysis of clinical trials	Recommendation B iii; University of Edinburgh's Research Strategy; Usher Institute Strategy 2020-2023	Number of ongoing methodological research projects
1.9. Capacity to develop and design clinical trials by growing the methodologist workforce within ECTU to further develop a Research Design Service for clinical trials	Recommendations B i and iii; Recommendation E; Usher Institute Strategy 2020-2023	Existence of a Research Design Service
1.10. Cultures and behaviours that respect and support people conducting clinical trials	Recommendation G; Usher Institute Strategy 2020-2023	Survey of working culture and behaviour
1.11. Equality, diversity, inclusion, expertise and support in all communities of staff supporting and conducting clinical trials	Recommendation G; Usher Institute Strategy 2020-2023	Survey of diversity
Design		
2.1. Clinical trials with methodological rigour and low risk of bias, informed by proof of concept, feasibility/pilot data, and patient/carer/public involvement	Recommendation B iii; Usher Institute Strategy 2020-2023	Quantification of methodological attributes of funding applications for clinical trials

Clinical trials strategy	Relevant strategy (appendix) or review recommendation(s) (pp. 1-2)	Suggested metrics for monitoring
2.2. With internal peer review and quality control, wherever possible	Recommendations B i and iii; Recommendation C i	Proportion of funding applications for clinical trials that undergo internal peer review
2.3. Clinical trials including methodological innovation and embedded studies into trial methodology where appropriate	Recommendations B i and iii	Proportion of trials that include methodological innovation or a study within a trial (SWAT)
2.4. Processes to develop and deliver clinical trials that are effective, streamlined and tailored to available capacity	Recommendations B i-iv	Quarterly assessments of capacity in ECTU
2.5. Clinical trials that are efficient, and economically, environmentally, and socially sustainable	University of Edinburgh's Strategy 2030; University of Edinburgh's Research Strategy; Usher Institute Strategy 2020-2023	Estimated carbon footprint of trial portfolio
Deliver		
3.1. Phase 1 clinical trials in the Edinburgh CRF	Recommendation C i	Proportion of Edinburgh's phase 1 trials that are delivered in the Edinburgh CRF
3.2. Phase 2-4 randomised clinical trials in ECTU	Recommendation C i	Proportion of Edinburgh's phase 2-4 trials that are delivered in ECTU
3.3. Clinical trials with the highest standards of research integrity	Recommendation B iii; University of Edinburgh's Strategy 2030; University of Edinburgh's Research Strategy; Usher Institute Strategy 2020-2023	Proportion of trials in which research misconduct has occurred

Clinical trials strategy	Relevant strategy (appendix) or review recommendation(s) (pp. 1-2)	Suggested metrics for monitoring
3.4. Clinical trials with sufficient resource to avoid over-burdening staff	Recommendation B; Recommendation C i	Staff survey of wellbeing in ECTU and ACCORD (including reporting to the NHSL/UoE strategic clinical research oversight Board and the UoE CMVM clinical trials oversight committee)
3.5. Within the staffing capacity in ECTU, ACCORD (e.g. research governance, global health, and pharmacovigilance), and other research facilities	Recommendations B i, ii, and iv	Staff survey of wellbeing in ECTU and ACCORD
3.6. Education and training for staff supporting the clinical trials pathway in Edinburgh to deliver cutting edge clinical trials	University of Edinburgh's Strategy 2030; Usher Institute Strategy 2020-2023	Number of educational opportunities provided
3.7. The clinical trials pathway with support from an ECTU clinical advisory group and oversight from a clinical trials strategy committee	Recommendation C ii	Existence of an ECTU clinical advisory group and a clinical trials strategy committee

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Comments on the final draft were received from: *Michelle Steven, Steff Lewis, Chris Weir, Peter Hall, Gina Cranswick, Tim Walsh, Charles ffrench-Constant, and Catherine Elliott.*

Appendix: research strategies within the University of Edinburgh

The University of Edinburgh's Strategy 2030 describes the University's vision, purpose and values, and its focus on people, research, teaching & learning, and social & civic responsibility. The focus on research states, "*We will strengthen our ability to generate new knowledge through primary research and provide ever better education and training for exceptional* ***early career researchers****. We will be the catalyst for new* ***industry*** *programmes and businesses that deliver benefit to societies around the world. We will do all of this while being critically aware of the* ***ethical, legal and regulatory responsibilities*** *of research. We will openly communicate our research findings to the public, governments and funding agencies. We will strive to make our research even more* ***interdisciplinary*** *and* ***international****, to address* ***social and global challenges*** *including the United Nations Sustainable Development Goals. We will create initiatives in a variety of areas including justice,* ***data science****,* ***environmental sustainability****,* ***mental health and wellbeing****,* ***ageing and dementia****,* ***human rights****, and* ***global governance****, driven by new* ***collaborative*** *research communities. Working in open facilities, researchers, students, the public sector and companies will 'breathe the same air' and solve major challenges side by side."*

The University of Edinburgh's Research Strategy was last published in July 2017, when it emphasised **interdisciplinarity**, **internationalisation**, **inclusivity**, **early career development**, **integrity**, **impact and partnerships**; three approaches were emphasised for delivering this vision, namely influencing **globally** & contributing locally, partnering with **industry**, and **digital transformation**. It seems likely that the pervasive underpinning approach for the University's research strategy for the next decade will be 'data-driven innovation', which is the cross-cutting strategic initiative that informs and drives developments in five over-arching research themes that involve all Colleges. Reflecting UN Sustainable Development Goals and the Scottish context, these are: (1) future health and care, (2) one health and food security, (3) societal and planetary sustainability, (4) culture and creative economies, and (5) living and working digitally.

The College of Medicine and Veterinary Medicine's 'One Medicine, One Health' strategy recognises that the College is the UK's only unified College of Medicine and Veterinary Medicine. Research programmes within the College explicitly link biomedicine and veterinary medicine, promoting the concept of "**One Medicine**". The research approach ranges from molecules to man, from bench to bedside, from process to population - and 'from lab to labrador.' The College is committed to recruiting and retaining the most talented **early career researchers**, and developing our culture of **translation of research** to maximise impact on health and wealth.

The Usher Institute Strategy 2020-2023 describes a mission to work with people, populations and their data to understand and advance the health of individuals and populations through innovative collaborations in a global community. The aims are to: nurture and support a **community** of skilled people contributing to improving local, national and **global health**; create a vibrant, nurturing **learning environment**, based on research-led, student focussed teaching; support open **collaborations** across and between disciplines to deliver **high quality, data-driven research**; **connect** with communities of policy makers, practitioners, patients, publics and other stakeholders to create, develop and share knowledge; and **innovate** to find new ways to address pressing issues in health

and social care. The principles are: **excellence** in learning and teaching, research, innovation and knowledge exchange; working to the highest ethical practices with **integrity**; a **team science** approach working with colleagues across academia, health systems, and communities to promote the well-being of individuals and societies; creating a **respectful, inclusive** working environment that supports colleagues in achieving their highest aspirations; developing equitable and sustainable relationships with communities locally, nationally and globally to ensure our work is responsive to their needs; continuous, **critical reflection and striving for improvement** in all that we do.