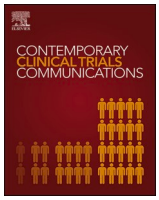
Contemporary Clinical Trials Communications 39 (2024) 101301

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Levelling the playing field through the London Network of the UK clinical trials accelerator platform

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A B S T R A C T

Cystic fibrosis (CF) is a multisystem, genetic disease with a significantly reduced life expectancy. Despite substantial progress in therapies in the last 10–15 years, there is still no cure. There are dozens of drugs in the development pipeline and multiple clinical trials are being conducted across the globe. The UK Cystic Fibrosis Trust's (CFT) Clinical Trials Accelerator Platform (CTAP) is a national initiative bringing together 25 UK based CF centres to support the CF community in accessing and participating in CF clinical trials. CTAP enables more CF centres to run a broader portfolio of trials and increases the range of CF studies available for UK patients.

There are four large specialist CF centres based in London, all within a small geographical region as well as two smaller centres which deliver CF care. At the launch of CTAP, these centres formed a sub-network in a consortium-style collaboration. The purpose of the network was to ensure equity of access to trials for patients across the UK's capital, and to share experience and knowledge. Four years into the programme we have reviewed our practices through working group meetings and an online survey. We sought to identify strengths and areas for improvement. We share our findings here, as we believe they are relevant to others delivering research in regions outside of London and in other chronic diseases.

1. Introduction to cystic fibrosis

Cystic fibrosis (CF) is an inherited disease which affects multiple organ systems. People with (pw)CF experience thick, viscous secretions in the airways, gastrointestinal (GI) and reproductive tracts leading to progressive damage, most notably in the pancreas leading to exocrine pancreatic insufficiency (PI) and the lung where progressive bronchiectasis and fibrosis leads to respiratory failure. Substantial increases in life expectancy have arisen from improved, earlier diagnosis and therapies. Once regarded as a disease of childhood, now, over half of the 10,000 pwCF in the UK are adults [1]. Despite these improvements, the median age of death in the UK remains low at ~38 years [1].

For decades, incremental improvements have been achieved with the development of therapies directed at the downstream consequences of CF, for example clearance of airway mucus, antibiotics for lung infections and pancreatic enzyme supplementation to improve fat absorption. In the last 10–15 years, enormous progress has been made following the development of the first treatments to target the basic defect itself. These drugs, known as Cystic Fibrosis Transmembrane Conductance Receptor (CFTR) modulators are "mutation specific", meaning that they only work for people with certain mutation types. They have been developed and tested through international trials

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https://doi.org/10.1016/j.conctc.2024.101301
Received 12 December 2023; Received in revised form 17 April 2024; Accepted 21 April 2024
Available online 26 April 2024

networks and have been shown to improve lung function, quality of life and nutritional parameters as well as reducing respiratory exacerbations and other CF related complications [2] [–] [4]. Real world data are starting to show a substantial improvement in life expectancy [5]. However, these drugs are not suitable for all pwCF and, as many who have commenced treatment already had significant irreversible organ disease, they are not a 'cure'. Therefore, clinical trials of new drugs will be needed for the foreseeable future.

2. Current state of play with new treatments

The trials pipeline in CF has been extremely active over the last decade. Since 2011, four CFTR modulator agents have been approved, all by the same company, Vertex Pharmaceuticals. There are ongoing trials studying the safety and efficacy of these licensed CFTR modulators in younger children as well as trials of newer modulator agents from multiple sponsors. In addition, there are essential trials of novel drugs that target downstream inflammation, infection and mucus clearance from preclinical to phase 4 trials [3].

3. How trials networks globally have delivered to date

The CF-specific trials networks seek to promote high-quality research to bring new therapies to pwCF as quickly and safely as possible. The Therapeutics Development Network (TDN) was founded in North America in 1998 and to date has conducted more than 150 clinical trials [2]. Ten years later, in 2008, the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN) was launched. It currently has 57 member CF centres in 17 European countries, which cover 21,500 adults and children with CF [6]. In 2021, the ECFS-CTN supported 28 CF trials and enrolled 529 pwCF [7]. The networks use multiple strategies to achieve their aims: working with patient organisations; centralising trial protocol reviews; supporting study conduct in its member sites; providing staff training; conducting study feasibility surveys; and standardising research procedures and outcome parameters.

4. Launch of CTAP

In 2022, 11 UK sites were a part of the ECFS-CTN. Although this makes up approximately a fifth of the 57 CTN sites, it still left approximately 20 UK-based sites without trials network membership [8]. Like much of the world, in the UK there are noticeable health inequalities between regions [9]. There is evidence that increasing health resource allocation to more deprived areas reduces the gap in health outcomes between the most affluent and most deprived regions [10]. One of the main aims of CTAP is for a broader population in the country to have access to CF trials, benefitting both the CF centres and their patients. Prior to CTAP's launch, some of the other UK centres lacked resources, experience, or both to conduct trials of investigational medicines. Others were research active, but predominantly conducting investigator-led studies and less frequently selected for pharma-sponsored interventional drug trials. The UK-based Cystic Fibrosis Trust (CFT) recognised the inequity in access this landscape provided, both to pwCF and the centres caring for them, and that the situation was to some extent self-perpetuating, with sponsors returning to sites with whom they had a track record. To address these issues, the Clinical Trials Accelerator Platform (CTAP) was launched, directed by the CFT with funding from the North American Cystic Fibrosis Foundation (CFF). CTAP aims to support more UK based CF centres to run a broader portfolio of trials, enabling participation by more people with CF in different regions of the country. The programme seeks to ensure the UK is at the forefront of global efforts to develop life-changing new therapies for people with CF.

Since its launch in 2017, the initiative has supported over 2600 children and adults with CF to participate in clinical trials across 25 UK-based centres (Fig. 1). The following 5 workstreams highlight the key areas of the CTAP's work:

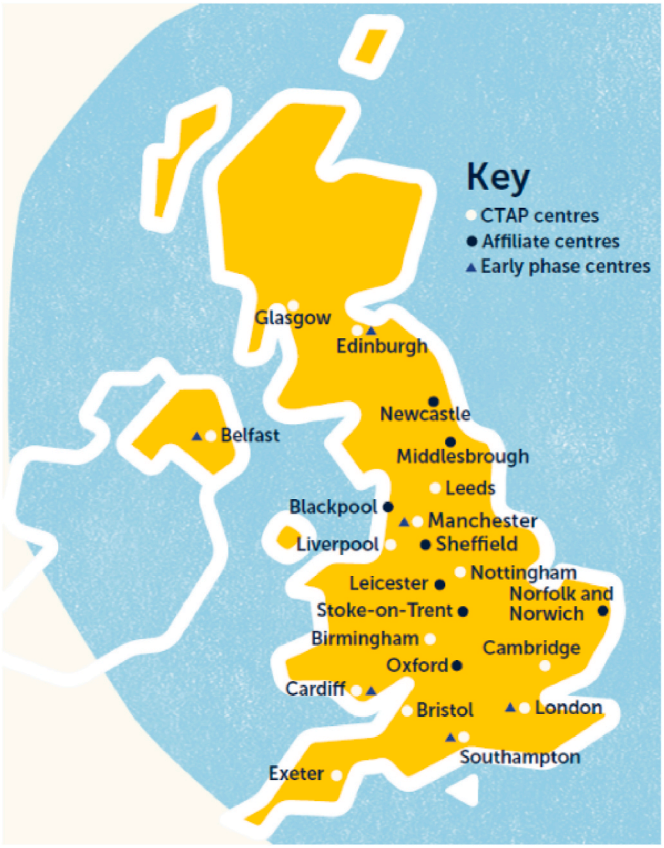

Fig. 1. Map showing the regional distribution of CTAP centres throughout the UK.

1. **Network of centres:** 25 CF centres were competitively selected to form the CTAP network, providing coverage to approximately 90 % of the UK CF population.
2. **Network of CF Trial Coordinators:** CTAP funds 19 CF Trial Co-ordinators based at selected centres throughout the UK who oversee trial set-up and recruitment as well as seven Early-Phase Co-ordinators at sites with phase 1/2 trial experience.
3. **CF Ambassadors:** CTAP recognises the importance of Patient and Public Involvement (PPI) in research, and that research should be performed *with* patients, rather than *on* them [11]. Therefore, CTAP has recruited over 200 pwCF and parents of pwCF to support PPI in CF research. These Ambassadors act as a representative voice for the therapeutic needs of the CF community and collaborate with sponsors to make recommendations on trial design and outcomes, ensuring there is a focus on what is important to pwCF.
4. **Sponsor Engagement:** CTAP supports both commercial and academic sponsors with the design, planning and identification of suitable recruitment centres from the CTAP network, in addition to facilitating engagement with the PPI CF Ambassadors.
5. **CF Clinical Trials Hub:** Hosted on the CFT's website, the Hub has a suite of information about trials, including a clinical trials information booklet, case studies and the CF Trials Tracker database which lists CF trials open in the UK (https://www.cysticfibrosis.org.uk/trialstracker) [12].

5. Governance and operations

The CTAP programme is governed by the Research and Scientific Oversight Board (RSOB), a multidisciplinary team (MDT) of leading CF clinical experts, CF Trial Coordinators, pwCF and parents of children with CF, and a senior statistician. The RSOB provides strategic

leadership to the CTAP programme, supporting delivery and development of objectives, in addition to providing a protocol review service to commercial and academic sponsors. Crucially, this work is delivered collaboratively with the ECFS-CTN; CTN adopted studies are automatically put on the CTAP portfolio. Frequent meetings between the two organisations ensure that activities take place in a complementary rather than competitive fashion.

6. The London Network and CF care

CF care in London is delivered by four large specialist centres (Royal Brompton Hospital, King's College Hospital, Great Ormond Street Hospital, and Barts and The Royal London Hospitals) and two smaller sites (Frimley Park and University Hospital Lewisham). They provide care to over 2000 pwCF, ~1100 adults and ~900 children, approximately 20 % of the UK's CF population. When CTAP launched, centres were invited to apply for membership and support with coordinators' salaries. Rather than submit parallel applications, with centres potentially missing out on opportunities through competitive applications, the London centres applied together in a consortium-style. Funding for 2.8 full-time coordinators was awarded between the four large centres, with the smaller centres joining the network as participant identification centres (PIC)s rather than conducting trials on site.

The London Network is the first regional sub-network within CTAP and operates a "Hub and Spoke" model. Prior to the London Network, The Royal Brompton Hospital had >20 years' experience delivering commercially sponsored CF trials with informal referrals of external patients, including those from as far as Ireland. When the 2006 gene therapy trial [13] opened at the site, a formal PIC system was introduced to establish a streamlined external recruitment process. King's College Hospital also had previous experience in delivering such trials, whereas Barts and The Royal London Hospitals and Great Ormond Street Hospital had less commercial experience, though the latter had run a highly successful pan-London academic paediatric collaboration for over a decade [14,15].

7. How the London CTAP sites function as a network

Communication between sites is paramount for the effective running of the network. The network holds monthly teleconferences with the sites' clinical leads, the London-based Trial Coordinators, and CTAP representatives to enable open discussions around optimisation of their clinical trial sites. The London Network centres work collaboratively and cohesively across the capital to ensure that CTAP's primary ethos, "equity of access", is met. The main aspects of the network are (a) cross-site support with knowledge and skill sharing and (b) the inter-site referral system.

Not all studies are suitable for an inter-site referral approach; we consider each trial individually. This model is adopted for one of two reasons: a) a small or rare patient population meaning recruitment of desired numbers from a single site is unlikely to be achievable or b) a highly desirable trial (for example, first access to a new drug). The referral system offers sponsors the opportunity to open a trial at a single, designated lead trial site whilst still having access to the entire CF population of London and the surrounding counties. Referring patients between sites also means that desirable trials, which may enhance the status/reputation of the centre, can be undertaken by newer sites allowing them to improve their experience and expertise. "Complementation not competition" is therefore our secondary ethos.

Global, multicentre studies, particularly those of CFTR modulators, may be highly competitive. Sites are restricted to the number of slots available, although there is progress towards this number being proportionate to the population served, something strongly supported by the CF community [16]. No universally acceptable solution has been found to how teams "choose" which patients are offered a screening slot for this type of trial [16,17]. Currently, the London Network assigns slot (s) to each participating centre, who select potential participants from a list of their site's eligible patients using a random number generator.

Before a trial can start, PIC agreements are set up between the relevant Research and Development (R&D) departments. Once a site is given the green light to open, potentially eligible patients can be formally referred between sites. Patients and/or their families give consent for this sharing of contact details and clinical information. Depending on the sponsor requirements, the referring site will need to provide written details about the patient's medical history and eligibility for the trial, for example, current medications and recent pathology results. Communication before, during, and after the trial is key to ensuring patient safety. Throughout the trial, the referring site are sent updates from each trial visit with any unblinded results shared and clinical concerns highlighted. There is an upfront agreement that this inter-site referral is purely for study visits and not for clinical care, which remains at the patient's original site. Any initial concerns that clinics may "lose" patients to trial sites due to the frequency of visits and the building of strong relationships between patients and trial staff have not materialised. Since the launch of CTAP, the London Network has enrolled 483 people with CF (223 adults and 260 children) to 39 different trials. This involved screening 780 pwCF (400 adults, 380 children) and 34 PIC referrals across the network. Referrals therefore account for ~7 % of all trial recruits, but are becoming more common as our experience grows.

8. Does working together work?

Two years after the London Network was established, investigators and coordinators came together with CTAP team members at the CFT, including the Public, Patient Engagement & Involvement (PPEI) representative, to identify the strengths of the approach and areas which could be improved. This took the form of an on-line survey and discussions at network meetings. The learning points are summarised below as trials teams in other regions, or those focussed on other diseases, may find useful parallels for their own research delivery.

9. Perceived strengths for patients

The main benefit for patients is perceived to be access to trials being more equitable. Without the network patients could only access a trial if it opened at their clinical centre. Access to highly sought-after trials was a postcode lottery. Even when the trial drug itself is not the main driver of patient participation, having the chance to be involved with research gives some the opportunity to fulfil altruistic needs, or to be a part of the research process and to learn more about their condition. Patients have been shown to have better clinical outcomes when they participate in trials regardless of the intervention. This remains so when attempts are made to adjust for confounders such as the types of patients who tend to seek participation [18,19]. Possible explanations include increased knowledge about, and ownership of, their disease leading to improved adherence and self-management [20]. Trial participation may also benefit psychological well-being, with patients involved in research reporting increased empowerment and self-esteem [21,22]. Without networks such as CTAP, pwCF at centres without access to research may not have the opportunity to reap these benefits. In addition, for subjects who may have been have asked to participate in multiple trials, having a network with a greater pool of patients reduces trial fatigue at individual centres.

10. Perceived strengths for staff

The London CTAP Network facilitates an environment of close communication, collaborative working, shared learning, and support. The collective experience, ideas and viewpoints of a critical mass of clinicians, experienced Trial Coordinators and CTAP representatives who are open to listening and learning from one another, ensures

everyone is well educated and has up to date information on CF and CF trials.

Generally, the virtually-held, monthly network meetings are open discussions about the common issues of the network's CF trials portfolio. This can be anything from establishing timelines on current projects or recommending specialist services, such as ophthalmology, which may be needed for specific trials. Additionally, the meetings provide a platform for discussions of individual cases causing concern, for example, potential new adverse drug reactions and to ensure appropriate referrals are made. The group also utilises channels such as WhatsApp for lesser issues and updates-no patient sensitive information (e.g. names) is used in these more informal communications. These discussions cultivate important joint decision making, giving research teams crucial support.

CTAP Trials Coordinators in the London Network have a unique research role. Close relationships with neighbouring sites enable clinical skills, such as performance of Lung Clearance Index (LCI), to be shared and practiced. Discussions and idea sharing is also a huge support, particularly for example during the recent COVID-19 pandemic.

11. Perceived strengths for institutions

The network's Hub & Spoke model allows more efficient access to a wide pool of patients in a relatively small geographical area, giving increased confidence that recruitment targets will be met. Together with this being more attractive to sponsors, the network increases the experience, reputation and profile of CF centres across London in running trials. In turn, this increases the research portfolio of the centres, improving the metrics and raising the income this may bring.

12. Challenges for patients

The first potential challenge is the increased complexity in ensuring clinical safety in terms of timely reporting and discussion of adverse events, particularly those of a serious nature, with their clinical team. This is even more complex if the patient is under a shared care system with a local district general hospital as well as a tertiary centre different from the trial site. This can be overcome with "as needed" calls/emails but these could get overlooked or delayed by teams' busy clinical schedules, resulting in delays. To address this challenge, we supplemented these ad hoc calls by implementing a standard post-visit letter to alert subjects' clinical sites of the visit, any clinical concerns, samples obtained and date of next visit. We are discussing whether inclusion of shared care centre staff in the network's meetings is practical; scheduling may well be challenging.

Although some studies suggest it can be stressful for patients/families to attend trial visits in an unfamiliar environment and with an unknown team; in our experience, this usually resolves quickly after the first visits. We have identified and adhere to ways in which teams can ensure a more pleasant experience for trial participants [23]. What seems more important to patients is that they don't need to travel more than 1.5 h for their trial visits which poses both time and financial burdens, particularly as expenses are reimbursed in arrears [24]. Due to the geographical structure of our region, inter-site referral can still be achieved without travel $>$1.5 h, but could be more challenging for future networks set up over greater areas.

Thirdly, in terms of logistics, with local patients, we often take opportunities to incorporate clinic appointments with trial visits. When these activities are delivered by different sites, this opportunity is lost, thus more visits are required. To counter this, lessons learned from the COVID-19 pandemic have highlighted that trial visits do not necessarily need to be performed on site and a shift away from centralised towards home or hybrid designs may lessen this inconvenience [25,26]. When visits are necessary, we make the referring site aware of any upcoming trial visits and facilitate simple clinical assessments (e.g. blood tests) to mitigate the need for double hospital appointments.

13. Challenges and opportunities for improvement for staff

Being in a network involves the added complexity of setting up PICs and managing new patients on trials. Discussing and sharing patient information, for example by extracting and securely sending across source documents, trial updates and referral letters creates extra work and, therefore, requires extra time. This is especially challenging during a rapid recruitment phase with pressure from sponsors to recruit before tight deadlines. Our discussions include ensuring workload is evenly distributed between sites, with an equitable distribution of trials where possible, and ensuring additional work generated is reimbursed. We hope to improve further by a) creating a Standard Operating Procedure to define the operational and administrative processes required to allocate, set-up and conduct trials in the London Network and b) continuing to develop educational events where ideas and experiences can be shared.

PIC professionals are not on the delegation log of trials. However, they are all expected to be compliant with Good Clinical Practice (GCP). They are invited to the sponsor's site initiation visits (SIVs) and encouraged to discuss the protocols as they continue to provide the full clinical management of the patient and could have considerable input in a trial, not just in identifying participants, but in documenting and informing the trial centre of any untoward events, changes in management, etc. This is especially challenging if a third tier of care is added when the specialist PIC shares patient management with a local hospital in the Southeast region.

In any circumstance, coordinating a group of thirty plus staff members, all with their own other commitments and timelines, can be difficult and finding a time for all to meet is complex. In our case, this has been supported by the central CTAP coordinating team, but we also hope to have bi-annual in-person meetings for all London Network members as a way of establishing stronger relationships. We plan for the Trial Coordinators to work together on a quarterly London Network summary newsletter to help inform colleagues of progress and achievements.

We have witnessed a high turnover of CF Trial Coordinators since establishing the network, although it is difficult to know how specific to London and the current economic climate this might be. Employment on fixed term contracts may in part account for this. Establishing a sufficiently future-proofed funded system to support permanent contracts and/or professional progression for CTAP coordinators would likely improve employee retention. Further ideas include expanding the leadership or educational responsibilities of the coordinators by supporting them to present at professional conferences, developing their writing skills through co-authoring manuscripts for publication and leading on quality improvement activity and service development.

Finally, choosing to work as a network requires senior investigators to work collaboratively, at times exchanging personal aspirations for investment in the growth and development of less experienced members of the network. The metrics-focussed research environment in the UK and other regions may appear to disincentivise such collaborative behaviour; in our opinion, normalisation and recognition of consortium-style working is urgently needed.

14. Challenges and opportunities for improvement for institutions

Setting up PIC contracts and the associated paperwork is time consuming. Early on, this led to delays in some studies opening, recruiting and data sharing. There may be even more of a challenge when patients transition from paediatric to adult care during a trial if that requires the involvement of a new centre. We consider this is largely down to variations in practices between centres, particularly regarding R&D staffing and procedures. For example, we have learnt that contracts are exchanged most quickly when the lead site contracts with PICs, removing any requirement for the sponsor to contract with individual

PICs. Another example is in establishing standards for costs/reimbursement of activities that R&D departments can charge for PICs. As a network, we are seeking to document the operational approaches and challenges of each centre's R&D department. By continuing to standardise processes wherever possible, and having standard SOPs, we hope to reach a more streamlined, harmonised process.

There is a challenge of having valid "source data" in a trial involving patients from another PIC which continues to provide the routine care. When the trial and clinical management is in the same hospital, most of the source data would be documented and located on the electronic patient record (EPR) or medical notes. This would be easy for monitors to verify when in the same hospital but less so when the EPR is at another site. Currently, encrypted E-mail correspondence from the PIC to the study site suffices as "source data" but we are exploring a more formalised process.

Initially, some sponsors were reluctant to use PIC sites due to unfamiliarity with the process, which led to delays and unbalanced workloads. Additionally, the slot allocation provided did not always reflect the London Network's population size. Since setting up the London Network, we have seen some progress in both scenarios, with sponsors becoming more accustomed to the new norm of the London Network, although there is scope for further improvement.

15. Moving forward – what is next for CTAP networks?

CTAP plan to roll-out the London Network model to other regions in the UK. We hope the following advisory points will help this process run smoothly.

START NOW	
1.	Education at the start; establish how sites will be selected to lead on studies, what is expected of them if they do lead, and what is expected of PICs.
2.	Consider the governance process for sites in the network.
3.	Plan for the extra time required and factor this into job plans.
4.	Ensure clear pathways are agreed from the outset for patient referral.
5.	Ensure relevant R&D representatives are invited to meetings.
6.	Create SOPs for processes where beneficial.
COMMUNICATE	
1.	Learn from others, do not reinvent the wheel.
2.	Ensure there are regular meetings from the outset, create open communication channels.
3.	Ensure there is a wide coverage of the MDT and that all contributing hospitals have a representative.
4.	Collaborate with sponsors to ensure becoming part of a network does not effectively reduce trial slots allocated by sponsors to populations.
5.	Discuss and agree how slots will be allocated between sites.
BUILD RELATIONSHIPS	
1.	Set out to achieve a communal sense of purpose.
2.	Develop materials to help colleagues starting their trials experience.
3.	Set up an "away day" to build relationships, including a social aspect.
4.	Create a named buddy system for new Principal Investigators or coordinators distinct from the central CTAP team or sites.

16. Conclusions

As well as identifying the benefits of such a Network we have identified challenging areas and continue to strive to adapt our procedures and practice to combat such challenges. The London CTAP Network required significant work in set up, but this has been offset by substantial benefits to patients and our CF community. The experience of the London CTAP Network can be used to guide other regional and national trials networks, both within CF and other disease areas.

Funding statement

GD is supported by a Future Leaders Fellowship from UK Research & Innovation (UKRI), Grant reference: MR/T041285. All research at Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

JCD is supported by the NIHR through a Senior Investigator Award and the Imperial Biomedical Research Centre. The work of the Royal Brompton site is supported through the NIHR Clinical Trial Facility.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Professor Jane Davies has undertaken clinical trial leadership and/or Advisory Board and speaking roles for Vertex Pharmaceuticals, Boehringer-Ingelheim, Eloxx, Algipharma, Abbvie, Arcturus, Enterprise Therapeutics, Recode, LifeArc, Genentech, and Tavanta.

She has been awarded research grants from the UK Cystic Fibrosis Trust, Cystic Fibrosis Foundation, Cystic Fibrosis Ireland, EPSRC, NIHR and LifeArc.

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