

Unstoppable in the search for answers

Research Impact Report November 2022

Uniting for a life unlimited





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Foreword

Funding and supporting research that will benefit everybody with CF is at the heart of everything we do. We are guided by your research priorities. We won't stop until everyone can live without the limits imposed by cystic fibrosis.

Exciting discoveries made in the lab can lead to the development of life changing treatments. It can take a long time to yield results, but together we are making progress. This report gives some examples of the difference we're making together. As one united and unstoppable community. I hope that you find it an inspiring read and feel as hopeful for the future as we are.

The Trust funds world class research in a number of different areas, helping to take new treatments from the lab to the clinic. The journey to develop a new CF medicine begins in laboratory-based basic research, which is called the 'discovery phase'. This is where the 'lightbulb moments' can happen and ideas for potential new or improved medicines and treatments are discovered. The Trust funds and supports lab-based research in this area through our UK CF Innovation Hub, Strategic Research Centre and Venture and Innovation Award schemes and the CF AMR Syndicate.¹

After being extensively tested in the lab, which is known as pre-clinical development, a potential new medicine or treatment will be investigated through clinical research,



Cystic Fibrosis Trust Involvement

in clinical trials or clinical studies. Our Clinical Trials Accelerator Platform (CTAP)² provides the knowledge and infrastructure to attract and support CF clinical research in the UK. It has recently expanded to include an Early Phase Trial network. We're starting to see the impact that increasing the UK's clinical research capacity and capability in this way may deliver for the community with increasing opportunities to take part in trials for all people with CF. Above: How Trust-funded research activities and partnerships advance progress in the medicines pipeline

 $^{1.\} www.cystic fibros is.org.uk/the-work-we-do/research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-in-research/where-your-money-goes/how-we-invest-i$

^{2.} www.cysticfibrosis.org.uk/the-work-we-do/clinical-trials-accelerator-platform

I have hope that in the future, with the incredible advancements in the field of medical science, everyone in the CF community will truly be able to live a life unlimited."

CF researcher Alice, whose brother has CF

We know we can't do it alone. Working together is essential in research to help us solve the trickiest problems in CF. In this report, you can also read about the progress of the CF AMR Syndicate, a partnership between Cystic Fibrosis Trust, Medicines Discovery Catapult, and LifeArc that is making a real difference in accelerating the advancement of treatments through this medicines pipeline. (See diagram left)

People living with CF and their families provide great insight and knowledge at every stage of research. You are experts by experience, so we seek ways to incorporate your views and advice into what research we fund, how CF research studies are designed and conducted and how to keep research meaningful to the people whose lives it aims to improve. Our involvement group³ members are people from the CF community, volunteering to help us with a variety of research activities, regularly providing their voice and opinion. As an example, over the last few years they have been helping researchers shape their study to investigate whether exercise can replace air way clearance techniques as a form of physiotherapy. You can read more about how you've helped design their studies on page 16 of this report.

Whenever someone talks about success whether it's an athlete after a competition or a writer in the acknowledgements section of a book, almost without fail they will thank the team who got them to where they are. This is my opportunity to say thank you for your support in the achievements we're celebrating in this report. Thank you for everything that you do to support our research. Each and every one of you in the CF community has helped us make this groundbreaking research possible. For every penny you raised. Every focus group you took part in. Every steering committee you joined. For the long hours in the lab, or going the extra mile in setting up a CF clinical trial. A heartfelt thank you to all of you.

Dr Lucy Allen Director of Research Alice Collins

Dr Lucy Allen

We won't stop supporting world class research

Professor Andres Floto

We support world-class research to enable and accelerate the development of innovative and novel approaches for CF care and treatment.

The UK CF Innovation Hub on lung health is a world-class strategic research partnership between Cystic Fibrosis Trust and University of Cambridge. Its aim is to find new ways to prevent, treat and repair CF lung damage so that everybody with CF can live healthier and longer lives.

Non-tuberculosis mycobacteria (NTM), including Mycobacterium abscessus (M. abscessus), can cause an aggressive lung infection in people with CF that is extremely difficult to treat. Gaining a better understanding of NTM infection and the development of exciting new treatments for it are some of the aims of the Innovation Hub. *M. abscessus* can sometimes be cleared by the body without the need for treatment, but can often cause serious and hard to treat lung infections for people with CF. The treatments can last over a year, have uncomfortable and intolerable side effects, and are very disruptive to day-to-day life. For the CF team, this makes it tricky to know whether and when to start treatment, and which medication will work best.

Sara who has CF told us: "When I first got diagnosed with NTM, I was told that there was no 'go-to' treatment to tackle this bug. It was all a game of 'trial and error' and you may be lucky if the treatment worked and it got rid of the infection. But in most cases you were stuck with it. Now 13 years later I'm still growing it.

Research in this area is so important as it could lead to new medicines that are better at getting rid of this infection for good, and giving those who have it a better quality of life."

In a research paper in the prestigious journal 'Science' published last year⁴, Professor Andres Floto and colleagues within the Innovation Hub shared their findings on what makes these bacteria adapt into these infection-causing strains. This research could have a big impact on CF care in the future, helping to improve decisions on the type and timing of treatment when people with CF test positive for *M. abscessus*. In a follow up paper, published in 'Nature Microbiology' this year⁵, the team have now identified specific genetic changes that are associated with worse clinical outcome and which could be developed into a test to help with treatment decisions.

New insights into how *M. abscessus* infections are passed on

Scientists need to understand infection-causing bugs better to understand how infections are passed on (transmitted) and to design better treatments. Working with Professor Julian Parkhill and his team in the Innovation Hub, Professor Floto's group found that infection-causing strains of *M. abscessus* are passed on from one person with CF to another. They found this out by analysing the DNA of *M. abscessus* extracted from the microbiology samples from people with CF. Bacterial DNA from samples from different people with CF was a very close match.

The puzzle was that they found very closely matched samples of *M. abscessus* from people with CF in different countries: from people who had never met and had never been to the same clinic.

In a research study published in 'Nature Microbiology' last year they found evidence that the infection is passed to people with CF by people who don't have CF⁶. This is the first report making this link and is an exciting discovery, but many more studies are needed to look out how this might be happening in more detail.

"The aims of our research are to understand the biology of *M. abscessus*, how it works, how it causes disease and how it is passed on, but also to develop antibiotics to try and kill it," said Professor Andres Floto, Director of UK CF Innovation Hub at the University of Cambridge.

"The reason I got interested in *M. abscessus* was because rates of infection are increasing around the world and we didn't understand why. One reason why is that there's person to person transmission of the bugs. Another is that the bugs have evolved and adapted to living in the lungs of people with CF, which makes treatment really difficult."

Breakthroughs made by scientists are reported in scientific research papers. These reports provide new knowledge for other researchers and doctors to build on, helping to bring forward the day when everyone with CF can live a life unlimited. Since our first research strategy was published in 2013 our research has led to the publication of 287 papers directly as a result of our funding.



287 papers

published directly as a result of our funding since 2013

^{4.} www.cysticfibrosis.org.uk/news/researchers-discover-how-mycobacterium-abscessus-evolves

^{5.} www.cysticfibrosis.org.uk/news/pioneering-new-analysis-at-university-of-cambridge-brings-more-effective-treatments-for-0

^{6.} www.cystic fibrosis.org.uk/news/how-mycobacterium-abscessus-infections-are-passed-on-putting-the-pieces-together and the second se

We won't stop building strong partnerships and relationships

We know we can't do it alone. Working together is essential in research to help us solve the trickiest problems in CF. Effective collaborations promote and facilitate the sharing of expertise, problem solving and resource, making an even bigger difference for people with CF.

Our Strategic Research Centre (SRC) awards are a multidisciplinary approach to advancing our understanding of CF and knowledge of how to treat it. They bring researchers from within and outside the field of CF together. Since 2013 the Trust has supported 22 SRCs, bringing together 142 scientists and specialists from over 50 cities and 15 countries around the world.



"If you really want to understand what's going on in CF, these kind of partnerships are absolutely essential. The Strategic Research Centre has allowed us to make networks and links that mean we can make progress in lots of different areas. It is really making a difference. I can't thank the Trust enough and I can't thank the donors enough," said Dr Martin Welch, SRC Principal Investigator at the University of Cambridge.

Across the grants we fund, the Trust has leveraged £44million in additional funding. Half of this has come from co-funding partners as part of our collaborative Venture and Innovation Awards, where we have partnered with other medical research charities, universities, hospitals and companies. We have also received co-funding support from the CF Foundation in the United States of America for our SRC awards.

We've also developed partnerships with other charities such as RNID, Diabetes UK, and public funders such as NIHR and the Medical Research Council in joint funding calls.

A partnership to accelerate the development of better treatments for CF infections

To live long and fulfilled lives everyone with CF needs access to effective medicines to treat CF lung infections, both for those able and unable to benefit from CFTR modulators such as Kaftrio.

New medicines to treat these infections are urgently needed due to antimicrobial resistance (AMR). This is where medicines such as antibiotics stop working as infection-causing bugs adapt themselves to avoid the effects of the treatment.

There is an urgent need around the world to develop new medicines to treat infections that overcome AMR. However, medicines for CF infections need to be developed in a different way to medicines for other infections because of the environment within the lungs of people with CF. Some companies see the additional difficulties in developing medicines for CF infections as a reason to focus on other conditions, meaning that people with CF can get left behind.

This is where the CF AMR Syndicate comes in...

The CF AMR Syndicate is a partnership between Cystic Fibrosis Trust, Medicines Discovery Catapult (MDC) and LifeArc to accelerate the development of new medicines to treat CF infections. If newly developed medicines can work in CF, then we may be able to transfer the knowledge to treat more common conditions that provide a more profitable return on investments.

The idea is to make treating new CF infections, an exciting, attractive and easier area of research to work in – whether you are working in the 'discovery' end of the new medicines pipeline, or whether you are a biotech company seeking advice on the best ways to test a new medicine that would meet regulatory approval."

Dr Paula Sommer, Head of Research at Cystic Fibrosis Trust



Accelerating progress

A 'toolkit' of resources has been created by the Syndicate to address some of the obstacles in developing new medicines to treat CF infections. People with CF, CF teams, scientists, doctors and those involved in the regulatory approval of new medicines, were all involved in developing it. The toolkit includes:

• Target Product Profiles (TPPs)

The Syndicate led the development of patient-focussed 'checklists' or TPPs for medicines to treat CF infections. These will be used by the biotech and pharmaceutical industry to develop new medicines that meet the needs and requirements of people with CF.

• Strain guidance

The Syndicate are developing some guidance on which strains or variants of each bug to use in drug development studies to ensure the medicine is likely to be effective in the CF lung.

• UK CF Infection Biorepository (UKCFIB)

The Syndicate has created a virtual collection of the most relevant strains of CF-infection causing bugs, making it easier for all researchers to gain access to them. The development of the UKCFIB was supported by funding from the Trust and the CF Foundation in the United States of America.

• PIPE-CF Strategic Research Centre (SRC)

This SRC will create new and check existing methods to test the effectiveness of new medicines to treat CF lung infections, reducing the time and cost of the development of new medicines. The SRC is co-funded by the Trust and CF Foundation.

New partnerships strengthen the CF AMR Syndicate

To attract new researchers into working in CF research and encourage existing researchers to continue in this field, the Syndicate has recently developed new partnerships to provide funding which will allow researchers to move their ideas forwards.

A partnership between MDC and WeShare aims to provide initial funding to test out 'risky' ideas, to bring in specialist expertise at a difficult point in the studies in the lab, and support in completing final lab studies before moving a new medicine into clinical testing.

We announced that the medical charity LifeArc joined the Syndicate as a third partner in September 2022.⁷

"Being an active member of the CF AMR Syndicate's Steering Committee has enabled me to share my experiences of living with a chronic infection and use them to help shape the Syndicate's strategy. It's encouraging to know that drug and diagnostic projects developed by the Syndicate have been informed by people with CF, ensuring our needs and priorities are at their heart," said Abi who has CF.



Since 2013 the Trust has supported **22** Strategic Research Centres with 142 scientists and specialists from over 50 cities and 15 countries around the world

7. www.cysticfibrosis.org.uk/news/lifearc-joins-forces-with-cystic-fibrosis-trust-and-medicines-discovery-catapult-to-strengthen





We won't stop developing the UK's capacity to deliver CF research

We will continue to invest in researchers at all stages of their career, supporting the CF researchers of today and developing the talent of tomorrow. We will also build the infrastructure that can support and enable the delivery of research that makes a difference for everyone with CF.



To continue to advance our knowledge and understanding of cystic fibrosis and develop more effective ways of treating the underlying condition, its symptoms and complications, we need to attract, retain and support scientists and clinicians working in cystic fibrosis research. One of the ways we do this is through our Strategic Research Centres (SRCs).⁸

"Strategic Research Centres are a really wonderful mechanism of funding, bringing together scientists, particularly early career researchers for fantastically integrated science. They provide a forum for open exchange of ideas and collaborative working. The results are greater than the sum of the parts," said Professor James Shaw, CF-related diabetes SRC Principal Investigator.

An SRC award includes funding to train and support four or five early career researchers to work in the programme. This can be a student working towards their PhD research degree, or funding for a scientist continuing their research after their PhD. The network within the SRC programme gives them peer support and the opportunity for exchange visits within the SRC to learn new skills and get to know other researchers working in different areas. Since 2013 we've funded 113 early career researchers.

Lucia Nicosia is studying for her PhD in Dr Patrick Harrison's lab at University College Cork in Ireland. They're part of the Trust's 'Therapeutic gene editing' SRC led by Professor Stephen Hart.



Since 2013 we've funded 113 early career researchers

"I'm going to visit two different labs within the SRC within a month. I'm going to France to test if my experiments work in cells that are a closer match for the lung cells in people with CF. A few weeks later I'll visit a lab in London, where I can test if my genetic editing makes a working copy of the CF protein. Our research is giving people with CF hope, and I think that's just incredible," explained Lucia.

Dr Harrison added "The best way to solve any problem is by having lots of people involved, lots of collaborators with different skills. Working in an SRC network gives early career researchers such as Lucia lots of opportunities for exchange visits. She can bring back expertise in new techniques to our lab, and build strong relationships between labs. It all helps move our CF research along faster".



8. www.cysticfibrosis.org.uk/the-work-we-do/research/where-your-money-goes/how-we-invest-in-research 9. www.cysticfibrosis.org.uk/the-work-we-do/clinical-trials-accelerator-platform

Professor James Shaw

Our CTAP network: the difference it makes

All of the things that people with CF do every day to keep themselves well, whether it is treatments or health monitoring, will have been tested in clinical trials, to check they are safe and they work well to help improve symptoms or complications of CF. Trials are a truly collaborative effort between those designing and setting up the trial, those running the trial at different hospital sites within the study, and the people with CF and their families who have kindly agreed to take part.

Establishing a clinical trials network like our Clinical Trials Accelerator Platform (CTAP) can be beneficial to everyone involved in clinical trials. CTAP is a UK-wide initiative that brings together NHS cystic fibrosis (CF) centres to support people with CF to access and participate in CF clinical trials, it includes funding for 25 Trial Co-ordinators.⁹

Due to the substantial cost of investment for the organiser of the trial, known as the study 'sponsor', running a study in an already-established network can make it easier and quicker to set up a study. Which ultimately means getting new and approved treatments to people with CF faster. The time from gaining approval to begin the study, to screening and recruiting their first trial participant is known as set up time. Since CTAP began, set up time for CF clinical trials has been reduced by six weeks.

For the centres involved in running a clinical trial, it's an opportunity to learn and practice the latest methods of monitoring CF, and can be an opportunity to update their knowledge about the condition too.

Finally, for those who take part in clinical trials, it's a chance to find out more about their health and whether a new medicine may be beneficial for them, sometimes long before a medicine becomes available on the NHS.

To me, taking part in clinical trials means playing my part in the 'research relay race' against CF. The baton was passed to me by previous generations who trialled medicines and therapies I have benefitted from since I was a small child. I hope we can keep inspiring future generations to carry on picking up that baton, until the race is won."

Rob who has CF

Since it was established in 2017, our CTAP network has screened 1,339 people with CF to take part in a clinical trial, with 1,047 people being enrolled in 44 studies. Around 6 out of every 10 trials (29 studies in total) were to test medicines that restored the CF protein. Other studies investigated treatments for different aspects of CF including infections, and mucociliary clearance.

Types of study CTAP supports

Traditionally there are four main stages of clinical trial. They're known as phase 1 to phase 4 studies.¹⁰ Phase 1 trials, also known as early phase trials, are the first time a new medicine has been investigated in people. Trials may look at the practicalities of how the medicine is given and involve early checks on the medicine's safety

Phase 1 trials are particularly important for medicines that act in new and different ways, such as genetic therapies for CF. To encourage the planning for more Phase 1 trials in CF in the UK, the CTAP Research Scientific Oversight Board (RSOB) made the decision to extend the remit of the CTAP programme to create an early phase trial network. The programme is supported by a grant from the CF Foundation.



Since CTAP began, set up time for CF clinical trials has been reduced by



10. Taking part in clinical trials: A guide for people with CF, parents and family members, Cystic Fibrosis Trust 2017

"We want to ensure that trials of the next generation of CF medicines can proceed smoothly and efficiently to speed up new drug discovery, especially for those without Kaftrio. Being able to set up and deliver these studies quickly and safely is a major draw for sponsors and means these opportunities will be offered to patients in the UK. The early phase trials network of CTAP means that we are ready to do this," said Professor Alex Horsley, member of CTAP Senior Leadership Team, consultant at Manchester Adult CF Centre, and director of Manchester Clinical Research Facility.

Setting up CTAP's early phase network

Early phase trial coordinator posts were funded in six of the existing CTAP centres in Belfast, Edinburgh, Manchester, London, Southampton and Cardiff. These coordinators will be able to support early phase trials adopted by the network.

"The early phase coordinators have the specialist skills and capacity to support this type of trial conducted within the CTAP network. Early phase studies are often quite complex and therefore require more support from the trial coordinators in comparison to other studies. I'm delighted that, because of this new early phase network, we have had discussions about novel studies we haven't supported previously, from companies who haven't run trials in the CTAP network before," said Rebecca Brendell, Head of CTAP at the Trust.

Professor Alex Horsley

Since 2017, our CTAP network has screened 1,339 people with CF, with 1,047 people being enrolled in 44 studies





We won't stop involving the CF comunity every step of the way

Primo



The voices of those affected by CF are at the heart of everything we do. From defining our research priorities, to making vital funding decisions, your lived experience matters every step of the way.

The Trust's involvement group of over 100 volunteers contribute to a wide range of projects.¹¹ They play a vital role in our Clinical Trials Accelerator Platform and support the CF research community to develop new research studies. Since the start of the programme people with CF and their families have participated in 30 different opportunities to get involved in research each year. They have shared their lived experience and views in focus groups, review draft documents written by researchers and represent the CF community in steering groups for ongoing projects.

"When I saw an opportunity to join the Trust's involvement group, I was really interested in it, as I had enjoyed my experience of speaking about my CF in other campaigns," said Simon a member of the involvement group. "I'd never done any volunteering before. It was interesting to hear how different, and I mean wildly different, the experiences of different people with CF are. How people with CF have helped shape new research about airway clearance and exercise

People with CF have thick, sticky mucus in their lungs which is difficult to remove. To move and clear these secretions, physiotherapy, often in the form of arduous airway clearance techniques, is an important part of the daily treatment regime. People with CF are also encouraged to be physically active to help clear their lungs. This can add another burden to their treatment routine.

In 2017 the results of a project to identify the CF community's top 10 priorities for research were announced. One priority really stood out for researchers Dr Don Urquhart and Dr Zoe Saynor, it was 'Can exercise replace chest physiotherapy for people with CF?'.

"We did some work around five years ago about exercise for people with CF, but when the CF research priorities

I wanted to get involved as I had a strong motivation to give something back. I think the experience of supporting the Trust has given me more confidence at work too."

Simon a member of the involvement group

11. www.cysticfibrosis.org.uk/communityinvolvement

Dr Don Urquhart and Dr Zoe Saynor

came out, we changed our plans. This is what the CF community really wanted answered, so we focused on that", said Dr Urquhart, CF and exercise researcher at the University of Edinburgh.

Since then, Dr Urquhart and research collaborator Dr Zoe Saynor, exercise physiologist at the University of Portsmouth have been receiving regular feedback from members of the CF community involvement group as they developed their successful funding application to the NIHR.

The researchers knew that there was a big variation in what people think of as 'exercise' and there were also lots of different ways that people with CF do their physiotherapy.

After speaking to them in a focus group, members of the CF community helped the research team design a consensus survey, known as a Delphi survey, to agree on the types of exercise that could be compared to physiotherapy, to answer the question 'Can exercise replace physiotherapy'.

The findings from the survey were recently published in the scientific journal 'Thorax'.¹²

"For us the lightbulb moment was, if you're going to do exercise for airway clearance, or do an exercise to replace chest physiotherapy, you need to do a type of exercise that is going to loosen and move secretions - and not all exercise will do that. The involvement team gave us a huge amount of support in designing the survey – sense checking the questions we were asking, if we'd missed things out and checking if our wording was appropriate," said Dr Urquhart.

The research proposal was at a time when many people with CF were gaining access to CFTR modulators such as Kaftrio for the first time. Talking to the CF community confirmed to the researchers that this was still a relevant question to answer.



"People with CF told us that doing their physio is something that they've always been told to do. They wanted some evidence that it was OK before they gave it up", Dr Saynor said. "We believe that the support of the CF community for this project not only helped us design a project for people with CF, but was also essential in helping us get funding to do the study".

Other people's stories really inspire me. It was interesting to hear about other people's experience of exercise and physio. What someone else said about their physio really resonated with me. It made me think 'oh, it isn't only me then'. I find being involved in research really rewarding, and it's a lot of fun meeting other people. It's a nice feeling to see the results, knowing that you had a part it in, that your ideas and comments have been taken into account,"

Tonia who has CF and has been involved in shaping this study

12. Saynor ZL, Cunningham S, Morrison L, et al; Thorax Published Online First: 09 September 2022. doi: 10.1136/thorax-2022-219213

We won't stop uniting in research for a life unlimited. Join us.

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It is thanks to our incredible supporters, that we can continue to be at the cutting edge of CF research. Making breakthroughs and discoveries that change lives for the better. Now and in the future.

But we know this is just the start. Incredible progress has been made, but there is still a long way to go until everyone with CF can truly live a life unlimited.

Our long-term aim is to tackle the underlying cause of CF, leading the way in the development of innovative future treatments and care. We also will continue to fund research that will improve the health and wellbeing of people living with CF today, ensuring that the changing needs and priorities of the CF community are addressed every step of the way.

By the end of 2022 we'll know your current and immediate priorities for CF research, and we'll be working with you, researchers, clinicians and research funders to address as many of them as we can, as soon as we can.

We won't stop until we can all lead the lives we want. Until cystic fibrosis stops challenging, damaging or shortening lives. And you can be part of it.

Please consider making a donation for research today, to help us bring forward the day when everybody can live without the limits of CF.

cysticfibrosis.org.uk/donate





Cystic Fibrosis Trust is the charity uniting people to stop cystic fibrosis. Our community will improve care, speak out, support each other and fund vital research as we race towards effective treatments for all.

We won't stop until everyone can live without the limits of cystic fibrosis.

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