



cf TODAY

SEP-DEC 2011

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cf CYSTIC
FIBROSIS
TRUST

Gene Therapy Appeal

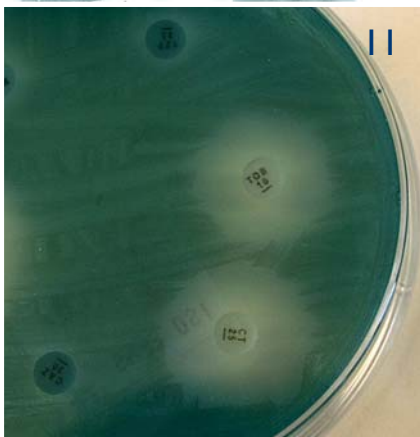
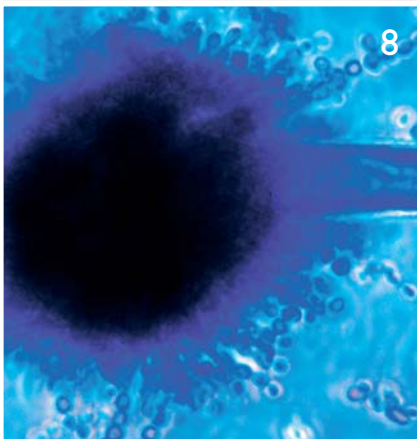
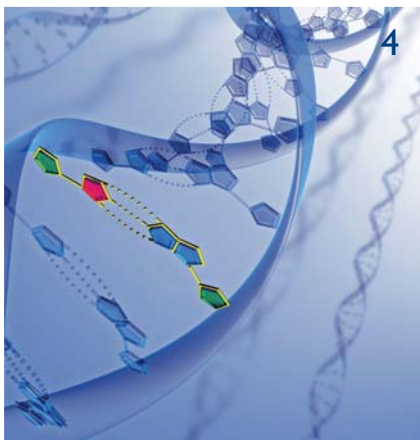
Research updates

Atypical Cystic Fibrosis

Clinical care

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The primary purpose of *CF Today* is to provide for its readers a reliable source of medical, research and other information relevant to Cystic Fibrosis and to play a supportive role for CF families. Opinions expressed in articles do not necessarily express the official policy of the Cystic Fibrosis Trust. The editor reserves the right to edit and otherwise alter articles or letters submitted to the magazine for publication.

Some pictures used in this publication may be posed by models or taken from library images.

Medical information included in this publication is not intended to replace any advice you may receive from your doctor or CF multidisciplinary team and it is important that you seek medical advice whenever considering a change of treatment regimen.

Cystic Fibrosis Trust
11 London Road, Bromley, Kent BR1 1BY.
Tel: 020 8464 7211 Fax: 020 8313 0472
www.cftrust.org.uk

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Editor: Jacqueline Ali

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Cover photo: Patient demonstrating nebulisation of gene therapy product, Royal Brompton Hospital, London
Photographer: Keith Gilbert

Welcome to this autumn edition of *CF Today*.

Thank you for all you did to make CF Week so successful in May this year. We were delighted with all the new activity, generating much-needed funds and raising the profile and public understanding of Cystic Fibrosis.

In this edition you will find updates on our campaign to protect frontline CF services from cuts, and developments in the treatment of CF with small molecule drugs. These and other developments are very important for our vision of significantly longer life expectancy and better quality of life for people living with CF today and their families.

You will also find an update on progress towards the world's first major clinical trial for a potential gene therapy treatment in the lungs of people living with Cystic Fibrosis. You will be aware that it was over ten years ago that the Cystic Fibrosis Trust first brought together the leading UK CF gene therapy researchers to form the Gene Therapy Consortium (GTC) and explore whether gene therapy could be a significant new treatment in Cystic Fibrosis.

Over the past ten years the team has developed and refined the gene therapy product, conducted toxicology studies, completed single dose pilot studies in some patients, and refined the dosage for the full clinical trial. The science, the patients, the trial protocol and the team are all now in place for this phase 2 clinical trial.

The work to date has cost substantially more than was first envisaged and at the time of writing we still do not have anything like the full £6million pounds required to undertake this clinical study. To me this feels like mile 24 of the London Marathon; we have come so far, but until we get to the finish line we haven't achieved what we initially set out to do.

The CF Trust and its supporters are therefore currently engaged in a Herculean effort to raise the full £6million pounds that the GTC needs before the end of this year. Without the funds in place this trial cannot proceed and without the trial we will not know the answer to the question posed a decade ago, namely whether gene therapy can be a significant treatment in Cystic Fibrosis.

Beyond this phase 2 trial there will still need to be a phase 3 trial, the costs of which could well be greater than the entire £30million already invested in this work, and therefore well beyond the CF Trust's capacity to fund. The GTC is therefore working to find a pharmaceutical company to take the gene therapy product into the next stages of testing.

"A Herculean effort is underway to raise the £6million needed for the gene therapy trial."

None of that will be possible though without the phase 2 clinical trial happening. Thank you for the huge amount that you are doing to get the trial funded and for your generosity. Even at this late stage please do let us know of contacts or organisations that could help with this enormous challenge.

Thank you for all you are doing in so many different ways to support the Trust's critical work. And kind regards from us all.

Matthew

Matthew Reed
Chief Executive



Matthew Reed

New clinical trials centres announced

The Cystic Fibrosis Trust-backed European Cystic Fibrosis Clinical Trials Network (CTN) has admitted two new UK centres. The Royal Brompton and Belfast will join Birmingham, Leeds and Nottingham to intensify clinical research in Cystic Fibrosis and to bring new medicines to the clinic as quickly as possible. The CTN works with the US Therapeutics Development Network, European patient organisations and industry to facilitate clinical trials in Cystic Fibrosis developments within Europe.

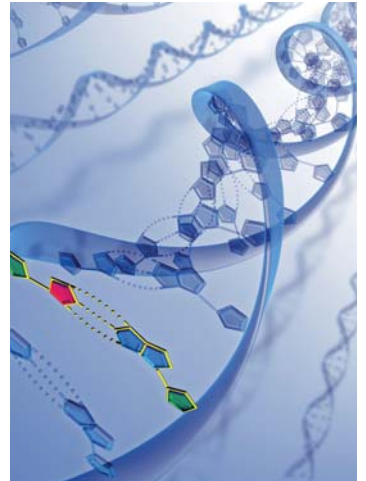


The Clinical Trials Network aims to speed up the development of new CF treatments

For further information about the Clinical Trials Network, see *CF Today* Apr–Aug 2011.

Pre-pregnancy genetic testing gains approval

In April this year, the Government's genetic advisory group approved the principle of genetic testing for couples before they conceive, in order to identify any genetic mutations they may have which could result in genetic diseases in their children.



Genetic testing involves screening DNA molecules for genetic disorders

The Human Genetics Commission (HGC) recommended that genetic testing be made available to all that want it, stating that 'there are no specific social, ethical or legal principles that would make preconception genetic testing within the framework of a population screening programme unacceptable.'

Currently only those pre-disposed to developing genetic conditions, for example those with a family history or from high-risk ethnic groups, are offered genetic testing on the NHS. In Cystic Fibrosis testing is offered to close relatives and partners of people with Cystic Fibrosis. Individuals or couples without a family history of CF can also undergo carrier testing but this is carried out privately.

The HGC report, entitled *Increasing options, informing choice*, states that individuals should be supported in making informed choices about the reproductive options available to them, and that if antenatal carrier screening is offered for a genetic condition then preconception screening should also be offered where possible. Testing would facilitate wider patient choice and improved access to information supporting reproductive decision-making, it says.

The Commission developed the guidance following a request from the UK National Screening Committee, which will now decide whether the recommendations should be introduced and if so, how they would be implemented.

Further information

Human Genetics Commission www.hgc.gov.uk

The Family Cascade Screening Programme for Cystic Fibrosis. CF Trust factsheet. Available from www.cftrust.org.uk/aboutcf/publications.

A detailed history of CF

Cystic Fibrosis Trust Chairman Dr Jim Littlewood has recently added the latest chapter to his online history of Cystic Fibrosis. This extensive work details the history of Cystic Fibrosis and the development of and advances in CF care and treatment since the first description of "fibrocystic disease of the pancreas" by Dorothy H Andersen in the 1930s. This fascinating and detailed account now includes the last decade 2000–2010. The History of Cystic Fibrosis can be found at www.cfmedicine.com/history.



The History of Cystic Fibrosis www.cfmedicine.com

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The early years

1595 From the mid-17th century there were many reports of infants who may well have had cystic fibrosis.

The first description of the pancreas in a child who almost certainly died with cystic fibrosis (CF) is usually attributed to Professor Pieter Pauw (1564–1617), the Professor of Botany and Anatomy at Leiden who wrote "On January 16th 1595, in a square leading to the Grand Canal in Treundeel, in the presence of Drs Trebaatus, Heurnius and Trutus, I conducted an autopsy on an 11-year old girl said to be bewitched. She had had strange symptoms for eight years. Inside the pericardium, the heart was floating in a poisonous liquid, sea green in colour. Death had been caused by the pancreas which was oddly swollen. It was very close to the rounded side of the liver, so that one could have thought, in touching it, that it was a scirrhus (a type of cancer with a hard and woody texture). When it was removed the interior was found to be brightly coloured, a kind of hard white viscous mass. The little girl was very thin, worn out by hectic fever (a fluctuating) but persistent fever".

The History of Cystic Fibrosis by Dr James Littlewood CBE

New charity partnership

We are delighted to announce that NHS Blood and Transplant will be a new charity partner of the Cystic Fibrosis Trust for 2011–13 after securing 239 of the staff votes.



Cystic Fibrosis Trust Chief Executive Matthew Reed said: "We are absolutely delighted that NHS Blood and Transplant have chosen us as their charity for the next two years and look forward to working in partnership with them." Staff members have already started to get involved in events, recycling and payroll giving and are committed to some great fundraising challenges ahead.

OBE for Rosie

We were delighted to learn in June that Rosie Barnes, former chief executive of the Cystic Fibrosis Trust, had been awarded an OBE for services to healthcare in the Queen's Birthday Honours List. Many congratulations from all at the Trust Rosie! You can read our tribute to Rosie in *CF Today* Sep–Dec 2010.



Rosie Barnes OBE

Seasonal flu jab

People with CF should make sure they get their annual flu jab each autumn. The seasonal flu vaccine is offered free of charge to at-risk groups to protect them from catching flu and developing serious complications. To find out more contact your GP or CF Centre, visit www.nhs.co.uk or call NHS Direct on 0845 46 47.

Award for CF Trust legacy campaign

The Cystic Fibrosis Trust was delighted to be awarded the Institute of Fundraising national award for 'Best use of Legacy Fundraising' at the prestigious annual ceremony in London in July. Beating off stiff competition from other national charities including RNIB, the *Rosie's Lasting Legacy* campaign was commended for being the most innovative legacy programme in the last 12 months. Congratulations to our marketing team and thank you to all who have helped make this campaign such a success. You can read more about legacy giving on page 15 – would you consider leaving a lasting legacy to the Cystic Fibrosis Trust?



Sarah Wheeler (left) and Sue Whitehead (right) from the CF Trust Marketing Department celebrate the award with Stephen George, Chair of Remember a Charity

Do your bit to safeguard CF care

Despite assurances from the Coalition Government that there will not be cuts to frontline NHS services, the CF Trust has uncovered a worrying trend of cutbacks across the country, putting CF services under threat.

Many specialist staff are being used to cover vacant posts on general wards, while others are seeing their working time reduced altogether. Posts are also being downgraded and, in some areas, maternity leave is not being covered, adding to pressure on other staff.

The CF Trust has launched a campaign to stop these cuts, calling on MPs to put pressure on the Government to comply with the agreed Standards of Care and staffing levels.

Cystic Fibrosis Trust Chief Executive Matthew Reed said: "We have seen fantastic improvements in quality and length of life for people with CF, but those improvements are at significant risk if these cuts are allowed to take hold. Specialist staff are filling the gaps where they can, but we cannot rely on hope and goodwill to maintain quality of care."

The Trust is asking all its supporters to contact their MP to ask them to sign parliamentary petition EDM 2033 and help reverse this worrying trend. More information can be found at www.cftrust.org.uk/aboutus/what_we_do/campaigns/nhscuts.



Parents Conference 19 November 2011

The Cystic Fibrosis Trust Parents Conference will be taking place on Saturday 19 November. The aim of the day is to provide an update on some of the key and emerging areas in Cystic Fibrosis research, treatment and care, and on the activities of the Cystic Fibrosis Trust.

Invites were posted over the summer to parents and carers on our database. If you have not received an invite and would like to attend, please email parentsconf@cftrust.org.uk or telephone 020 8290 7915. Further details can be found on our website www.cftrust.org.uk/aboutus/what_we_do/conferences.

Gene Therapy Appeal



The gene therapy product

At the time of going to press, progress on our Gene Therapy Appeal – to raise the £6million needed for the clinical trial planned for spring 2012 – was very encouraging. By early August, over £200,000 (excluding gift aid) had been donated by our community supporters alone.

Obviously £6million is a huge amount for our supporters to raise, and as such, it is hoped that the majority of the funds for the trial will be secured from major donors, trusts and corporate donors. The Cystic Fibrosis Trust is exploring all avenues both in the UK and abroad in order to make this happen.

However the continuing support of the CF community is also invaluable, whether through personal donations, fundraising activities or raising awareness. Your support has helped build momentum for the Appeal and demonstrated to potential major donors just how important this research is to so many people.

Thank you for all you have done and continue to do to contribute to the Gene Therapy Appeal – your support really is making a real difference. There are now just a few weeks left during which we will have a final, big push on this Appeal. If you are able to help in any way or would like to make a donation, please see details overleaf for some ways in which you could contribute.

The clinical trial phases

The multi-dose clinical trial planned for spring 2012 is the culmination of ten years of research into CF gene therapy carried out by the UK CF Gene Therapy Consortium – research made possible by the efforts of our supporters.

So far, a **pilot study** has been carried out in small numbers of patients given a single dose of the gene therapy product. This showed that the product is safe, and helped determine the optimal dose for the multi-dose trial. In parallel around 200 patients have also been recruited in to the **run-in study**, in order to assess a new range of sophisticated and sensitive tests which will be used to measure the effect of gene therapy, and to decide which patients would be best suited to go through to the **multi-dose clinical trial**.

Following the completion of the run-in study, the multi-dose trial is now ready to commence next spring. This is a **phase 2** clinical trial, in which over 100 people at the Consortium sites in London and Edinburgh will be given either the gene

therapy product or a placebo, once a month for a year. For safety reasons, the starting times will be staggered so some patients will begin the trial later than others; therefore the trial will take around 18 months to complete. The results will then be analysed to see if patients show improvements in their lung function and other measurements over this time period.

If the trial is successful and the results confirm that the product is an effective treatment for CF in the lungs, the aim is to then find a pharmaceutical company to take the product into a **phase 3** clinical trial involving larger numbers of patients and likely on an international scale, to gather more information about the effectiveness of the treatment and any side effects. **Phase 3** trials usually mark the final stage of clinical testing, and the purpose is to gather enough data about a treatment to request marketing approval, manufacture the product, and make it available to patients. However sometimes regulatory bodies may request further studies are conducted if they are not convinced of the benefit to patients.

Further updates on the gene therapy appeal can be viewed by clicking 'latest gene therapy news' on our home page www.cftrust.org.uk.

What is the gene therapy product?

The gene therapy product that will be given to patients in the multi-dose trial is a mixture of two main components:

DNA – which contains the correct version of the CF gene

A **vector** (gene transfer agent) – which helps deliver the gene to the correct location in the cell.

The gene transfer agent or vector is composed of a lipid (fat), which has a positive charge. This binds with the DNA, which is negatively charged, so that the molecules are tightly bound together and don't disintegrate when the product is nebulised. Upon nebulisation, the product is taken up by cells in the respiratory tract, where the correct copy of the gene should start to express itself.

Ways you can help

Donate

Visit www.virginmoneygiving.com/cysticfibrosisgenetherapy-1 to donate online.

Donate via **JustTextGiving**: text **GENE06 £5** to **70070** to donate £5 or **GENE06 £10** to donate £10 to the Appeal.

Spread the word

Why not **Tell 6** people about our campaign? Help raise awareness of this important work and encourage friends, families, colleagues or anyone else to donate!

Organise or take part in a fundraising event

How about organizing a coffee morning, jumble sale or fun day to raise funds for the appeal and have a great fun day in the process? We can provide lots of support to help you – visit www.cftrust.org.uk/help/howtoorganiseanevent.

On our website, you can also find out about some of the fantastic and fun events you can take part in to raise funds. Runs, walks, bounces, bakes – there's something for everyone. Visit www.cftrust.org.uk/help.

Could your company help?

Would your company consider supporting our campaign? Perhaps by holding a non-uniform day, cake sale or by making a donation? Visit www.cftrust.org.uk/help/fundraising-at-work or email corporate@cftrust.org.uk for more info.

Could your child's school help?

We've enlisted Oli and Nush, stars of *Getting Nosey about CF* – to encourage schools to support our Appeal (see below).

Could your school raise £600 in 6 weeks

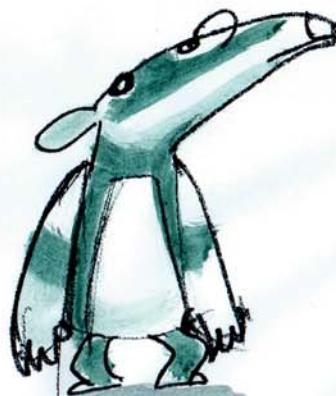
As part of the Gene Therapy Appeal, we have developed a postcard based on our *Getting Nosey about CF* DVD, for any schools that may be interested in helping to raise funds for the Gene Therapy Appeal.

If we could encourage just over 9,000 schools (one school for every person living with CF in the UK) to take part in our '£600 in 6 weeks' challenge – we could raise the £6million needed for the trial!

If you or your child or a friend or relative with school-aged children could take the postcard into school during the first week of autumn term and encourage the school to take up the challenge, we would be delighted to support them with their fundraising. We can provide a lesson plan and presentation, colouring in sheets, fundraising ideas, Big Cake Bake packs or just some posters and balloons!

Postcards are enclosed in the current edition of *Inspired!* If you don't receive *Inspired!* you can order a postcard by contacting the events team.

For more information call our events team on **0300 373 1100**, email events@cftrust.org.uk or visit our website www.cftrust.org.uk/oliandnush. Please get in touch and let us help your children's school to raise **£600 in 6 weeks** – all towards our £6million Appeal.



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Ask the expert

Ask the Expert is the Cystic Fibrosis Trust's expert advice service for people with Cystic Fibrosis and their families. Questions are answered by a panel of clinicians who specialise in different areas. Although your query and the response may appear on the Cystic Fibrosis Trust website or in this magazine, your name and personal details will always remain confidential and will not be published.

Treatments for specific mutations

Q A relative with CF has the mutation F508del with 711+1G>T. I was wondering if there is any research being undertaken to help combat this mutation.

A One of the new approaches in drug development is to try to treat the disease at the protein level and different drugs must be developed to rectify the specific defects caused by different mutations. To this end, Vertex Pharmaceuticals is developing a drug called VX-809, which is designed specifically to correct the fault caused by F508del. The F508del mutation gives rise to a protein that does not even get to the cell membrane (where it is required) and so cannot possibly work. VX-809 allows the "chaperone" machinery in the cell to move the F508del CF protein to the cell membrane where it has some activity, even though it is still a defective protein.

In my opinion, VX-809 does show some promise although it might not get to market in its present form (see research update on page 10).

The other mutation in this patient, 711+1G>T, is what is called a **splicing mutation**, and results in a piece of the protein missing. At present, there are no drugs in the pipeline for this kind of defect, although the research being undertaken at the DNA level is very active.

For information on VX-809, visit www.vrtx.com/current-projects/drug-candidates/VX-809.html.

Acquisition of Aspergillus

Q My daughter has CF and my partner has Aspergillosis (but not CF) and is concerned about contact with my daughter. My partner has asked a consultant, who has assured us that this is not an issue as Aspergillus cannot be passed from person to person and is

generally found in the environment. Having done an extensive Google search on the subject myself, it would appear that there is no evidence for person to person transfer.

Can you confirm that it is ok for my partner to have normal contact with my daughter?

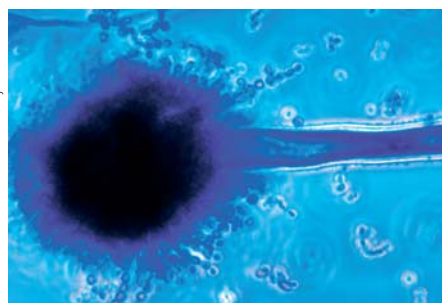


Photo: © CDC/Dr. Libero Ajello

Aspergillus is a fungus (or mould) that is very common in the environment

A We have no evidence of person-to-person spread for Aspergillus. Acquisition is most likely to occur from any one of the multiplicity of environmental sources. There is no reason to prevent normal contact between your partner and your child with Cystic Fibrosis.

Bugs in dishwashers

Q I saw on the news recently that dishwashers could harbour bugs that are potentially dangerous to people with Cystic Fibrosis. Is this something to be concerned about?

A You may have seen some articles in the press regarding fungi in dishwashers. Virtually any moist surface will harbour germs and most bugs including *Pseudomonas aeruginosa* are found in

environmental sites including washing machines, dishwashers, damp dishcloths etc. However although these sites harbour bacteria that does not inevitably mean they all present a serious risk of infection to someone with Cystic Fibrosis. In addition the fungi described in the news story – *Exophiala dermatitidis* – is considered to be a harmless coloniser of the airways of people with CF and there is no evidence to suggest it is pathogenic (harmful) in the CF lung. Life for CF families has to be a balance between unnecessary risk of infection and quality of life.

We would advise that people with CF and their families always use their dishwasher at the highest possible temperature to ensure eradication of as many organisms as possible, and also maintain and clean their dishwasher regularly in accordance with the manufacturer's advice.



Photo: © David Locke / Flickr

Using dishwashers at as high a temperature as possible helps eradicate micro-organisms

Our experts for this issue were:

Dr Jim Littlewood, Chairman, Cystic Fibrosis Trust

Members of the UK CF Microbiology Consortium

You can view an archive of past Ask the Expert questions at www.cftrust.org.uk/aboutcf/asktheexpert.

Please note if you have any queries or concerns about any aspect of Cystic Fibrosis you should contact your CF team in the first instance.

Submit your question to asktheexpert@cftrust.org.uk

European Cystic Fibrosis Society Conference – from the patient perspective

Cystic Fibrosis Trust Expert Patient Adviser Dominic Kavanagh was asked to speak at the recent ECFS Conference in Hamburg on the patient perspective of taking part in clinical trials. As Dom explains, the experience was both rewarding and thought-provoking.

I was asked to give a patient perspective on involvement in clinical trials, as part of the ECFS Clinical Trials Network (CTN) training day, at the European CF Society Conference (Hamburg, 8–14 June). My two-day trip, funded by the ECFS CTN, gave me a very interesting insight into my first ECFS Conference.

Delegates (mainly clinicians, scientists and other allied health professionals) descended on Hamburg in their hundreds, coming from all countries across Europe and some from beyond the EU. The presentations I attended, including ‘Clinical Trials in Young Children with CF’, and ‘Maximising the Value of Registry Data in Europe’ were very informative and created interesting discussion points. At the tender age of 44, the ‘CF Ageing Group Meeting’ also seemed an obvious meeting for me to join, where there was discussion on a questionnaire for the ageing CF population across the UK and Europe and how registry data could be used to give an overall picture of this patient group’s clinical status over the years – i.e. how were they when they were younger and how are they today as ageing adults with Cystic Fibrosis.

My presentation, ‘Clinical Trials – the CF Patient Perspective’, was based not solely on my experience of clinical trials, but also on that of others with CF who responded to my questions on the CF Trust’s Adult Forum (www.cftrust.org.uk/forum) and Expert Patient Adviser Facebook page (www.facebook.com/epacfftrust).



EPA Dominic discusses clinical trials from the patient perspective

trials, along with their advice on how clinical trial centres should present and conduct trials. Following my presentation, in tandem with a presentation from the Scientific Director of Vaincre La Mucoviscidose (French CF patient organisation) on the importance of the ECFS CTN for people with CF, we heard the perceptions on clinical trials of the pharmaceutical industry, followed by a US perspective on maintaining quality standards in clinical trials. A representative from the European Medicines Agency gave a presentation on training in regulatory requirements at clinical trial centres in Europe. Delegates then broke off into groups to discuss aspects of running clinical trials at a ECFS CTN site.

I spent some of the evening looking at products and literature on the pharmaceutical stands, represented by many of the key names we all recognise. The hearty German food and muggy conditions during my short time in Hamburg gave both my digestive enzymes and lungs a good work out!

Further information

European Clinical Trials Network. *CF Today*. Apr–Aug 2011. See also www.ecfs.eu/ctn.

www.cftrust.org.uk/research/clinicaltrials

CF News Network

You can keep up to date with the latest developments in Cystic Fibrosis research worldwide including CF conference highlights by subscribing to CF News Network (CFNN). This independent CF news portal contains a handy round-up of some of the key research news from across the globe, with expert comment by CF clinicians. Visit www.cfnewsnetwork.com to register for your free monthly e-newsletters.



Regulatory requirements at clinical trial centres was one of the conference hot topics

Some well-considered, detailed responses (thank you!) provided an interesting perspective for the audience of about 70 delegates, the majority of whom were either already part of the European CF CTN or aspiring to become a CTN site.

Fellow CF patients from the CF Trust’s forums gave me their view on clinical trials in which they’d already been involved. It was reassuring to hear UK CF patients’ opinions on factors which either encouraged or discouraged them from being involved in clinical

Vertex Latest

In the last *CF Today* we reported that VX-770, a CF drug in development by Vertex Pharmaceuticals and aimed at those with the G551D mutation aged six and older, had shown promising results in a phase 3 clinical trial. In June this year, further data presented at the European CF Conference in Hamburg showed that the reported 10% improvement in lung function was able to be sustained over a period of 48 weeks, indicating that the beneficial effects of the treatment are also long-lasting.

Vertex is now planning to submit applications for approval of VX-770 as a CF treatment in the United States, Canada and Europe including a Marketing Authorization Application in the European Union in the

second half of 2011. If approved, VX-770 could be licensed as a treatment in the UK as early as next year.

Interim data from a second Vertex clinical trial, investigating a combination of VX-770 with another drug, VX-809, were also released in June. This phase 2 study is investigating whether the combination of drugs is effective in those with the F508del mutation. However the

data were not as encouraging as hoped; results for one key measure – a reduction in sweat chloride (see box) – were lower than expected. Vertex intends to initiate the second part of this study in the fourth quarter of 2011.

The 'small molecule' approach

VX-770 and VX-809 are known as 'small molecule' drugs. These drugs have a low molecular weight and are usually easily absorbed into the body. Importantly for patients, this means they can be taken orally as a small tablet (in the trials, one tablet was administered twice daily).

Vertex's small molecule drugs are designed to target the root cause of Cystic Fibrosis – the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein – which is either missing or doesn't work properly in someone with CF depending on which mutation they have. CFTR is responsible for regulating the flow of chloride across the cell surface to help hydrate and clear mucus from the airways. Theoretically therefore correcting the action of this protein would allow sodium and chloride to move properly in and out of cells and prevent

The significance of sweat chloride

Raised sweat chloride levels are a diagnostic measure of CF, resulting from defective CFTR activity in cells in the sweat duct. People with CF typically have sweat chloride levels in excess of 60 mmol/L, while values in people who do not have CF are less than 40 mmol/L. Reduction in sweat chloride is considered to be a marker of improved CFTR function.



The Vertex drugs will likely be taken as a single tablet twice daily

the mucus build up which causes the damaging symptoms to the lungs and digestive system seen in Cystic Fibrosis.

As the two drugs in development by Vertex – VX-770 and VX-809 – are aimed at two different CF mutations, they have two different modes of action.

VX-770, which is targeted at the G551D mutation, is a **CFTR potentiator**. In those with the G551D mutation (around 4–5% of the UK CF population) CFTR is produced but doesn't follow instructions from the cell to allow chloride ions out. VX-770 *potentiates* the function of CFTR, i.e. increases the time it is open, helping it to behave normally once it reaches the cell surface.

VX-809, which is targeted at the F508del mutation, is a **CFTR corrector**. In those with the F508del mutation (over 90% of the UK CF population) the CFTR protein does not reach the cell surface in normal amounts. VX-809 *corrects* the production of CFTR, helping it to reach the cell surface where it is then able to function.

Further developments on the Vertex treatments will be posted on the CF Trust homepage www.cftrust.org.uk.

Further information

Vertex Pharmaceuticals www.vrtx.com

For more information about mutation classes in CF see *CF Today* Winter 2008/9.

Ataluren advances

Data were also released in June from a phase 2 trial of another CF treatment targeting the basic defect.

PTC Therapeutics' Ataluren (formerly called PTC 124) is effective against a certain class of mutation known as 'nonsense' mutations (normally ending in X, for example G542X), which prematurely halt the synthesis of CFTR, causing it to be too short and therefore not function properly. Around 10% of people with CF have at least one of these Class 1 mutations, and the therapy could also be applied to other genetic diseases involving nonsense mutations, such as Duchenne Muscular Dystrophy.

Data from the phase 2 trial showed that CF patients who took the drug (which is also an oral preparation) three times daily, had improved function of the CFTR protein (measured with an electrical test in the nose) and a decrease in the frequency of cough. Ataluren was also associated with improved lung function.

It is now being evaluated in a phase 3 clinical trial in Europe and North America.

Further information

PTC Therapeutics www.ptcbio.com

Gene therapy

Plans are in place for the phase 2 gene therapy trial to commence in spring 2012, subject to the required funding being secured. You can read about the gene therapy appeal on page 6.

Bronchitol on hold

An inhaled treatment to reduce mucus build up in the lungs of people with CF and other respiratory conditions has been put on hold after queries were raised about the effectiveness of the treatment.

In clinical trials, treatment with Bronchitol improved lung function in children and adults by 8%. However although

the treatment is licensed for use in Australia where manufacturer Pharmaxis is based, the Committee for Medicinal Products for Human Use (CHMP) rejected the company's application to market Bronchitol in Europe, citing concerns that while the drug seemed to work well in adult patients the results in younger patients were less consistent.

At the time of going to press, Pharmaxis had just submitted a formal request to the CHMP to re-examine their marketing application. And although Bronchitol may not be suitable for everyone with Cystic Fibrosis, many CF experts in Europe are supporting the re-examination. Dr Diana Bilton, Consultant Physician at the Royal Brompton Hospital in London, said: "We need to extend the treatment options and choice for people with CF and hope to see this treatment be made available."

How CF Trust grants can boost longer-term research

Readers of *CF Today* will be accustomed to seeing news about grants awarded by the Cystic Fibrosis Trust to fund research projects, which usually provide funding for two to three years of research. What you might not appreciate is how sometimes this is just the start of a process leading to much longer-term support for Cystic Fibrosis research.

In the past, I have been fortunate enough to receive grants from the CF Trust for research into the microbiology of CF infections; part of a long and fruitful collaboration with Dr Martin Walshaw and colleagues at the Adult CF Unit in the Liverpool Heart and Chest Hospital. In particular, the CF Trust, alone or jointly with the Big Lottery Fund, has supported our research into the Liverpool Epidemic Strain (LES) of *Pseudomonas aeruginosa*, which is a particularly problematic strain of *Pseudomonas*. Support from the Trust enabled two PhD students to complete degrees in CF research: Dr Catherine Smart (2002–2005) and Dr Jo Fothergill (2005–2008). Perhaps more importantly though, because of the success of our CF Trust-funded research, we were able to obtain further funding from a number of other sources.

More recently, in collaboration with others at the University of Liverpool (Dr Mike Brockhurst and Dr Steve Paterson), we were awarded approximately £500,000 in two separate grants from the Wellcome Trust, for a project lasting from 2009 until 2015. A further £150,000 was obtained from the Dr Hadwen Trust (2008–2012). Perhaps most significantly, when Liverpool was awarded a grant to establish the National Institute of Health Research's only Biomedical Research Centre on Microbial Disease (approximately £20 million, 2008–2012), one of the 15 projects being undertaken (led by myself and Dr Walshaw) was focused on various aspects of epidemic

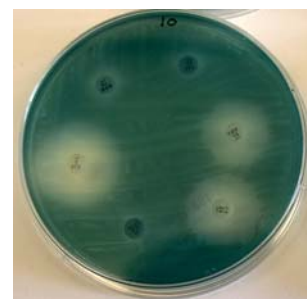
strains of *P. aeruginosa* in CF, and has enabled Dr Fothergill to continue working in CF research. The purpose of the Biomedical Research Centre (www.liverpoolbrc.org) is to facilitate projects that could translate into benefits for patients, and the projects cover a range of infections. It was important that we secured a place for CF infections amongst the portfolio of projects, and we wouldn't have been able to do this without the previous support of the CF Trust.

The work carried out has led to the development of better diagnostic tests and a clearer understanding of the LES.

Without the initial work funded by the CF Trust, we would not have been in a position to obtain this additional funding, and I'm sure that others involved in CF research have similar stories. Hence, be assured, that when you see the CF Trust list the research that it supports, this by no means represents the depth of CF-related research currently taking place in the UK, much of which was enabled by initial CF Trust grants.

Further details of CF microbiology research in the UK can be found on the website of the UK CF Microbiology Consortium www.cfmicrobiology.org.uk.

Craig Winstanley, Reader in Microbiology, Institute of Infection and Global Health, University of Liverpool



Agar plates are used to test for bacterial resistance to antibiotics

"Because of the success of our CF Trust-funded research, we were able to obtain further funding from a number of other sources."



Craig Winstanley, University of Liverpool

Atypical Cystic Fibrosis

'Atypical CF' is a form of Cystic Fibrosis thought to affect approximately 2% of all those with CF and is often characterized by less severe symptoms than seen in so-called 'classical CF'. However as Dr Kevin Southern at the University of Liverpool explains, atypical CF is not always easy to diagnose, with many patients receiving a diagnosis later in life.

What is atypical Cystic Fibrosis?

Atypical Cystic Fibrosis is the name used when a person has signs and symptoms that are consistent with CF but does not fulfill the strict rules that are used to make a diagnosis of Cystic Fibrosis. In most cases, this is because the amount of salt in the sweat is not high enough to make a diagnosis of Cystic Fibrosis.

As people with CF have a high concentration of salt in their sweat, the sweat test (where sweat is collected and the salt concentration measured) has been and remains an important part of making a CF diagnosis. This salt concentration is determined by the chloride value, which in people without CF is rarely above 30. A chloride value over 60 is considered consistent with CF, and many people with standard (sometimes called classical) CF have a much higher value. A chloride value between 40 and 60 in a person with signs and symptoms consistent with CF is often given the name atypical CF.

"In atypical CF, the CF gene is still able to do some of its work."

Is the term 'atypical CF' universally accepted?

Atypical CF is a controversial name and some feel that it shouldn't be used, i.e., that you either have CF or you don't. In North America, recent consensus guidelines on making a diagnosis of CF do not support the use of atypical CF, although in reality many physicians in the US do use the term. Atypical CF is more widely used in Europe.

How does atypical CF happen?

Nearly 2,000 different gene abnormalities (or mutations) have been recognised on the CF gene; it is not surprising therefore that some of these abnormalities are associated with less severe disease. These gene abnormalities do not completely stop the CF gene from working and it is able to do some of its job, controlling salt movement across cells.

Is being diagnosed with atypical CF a good or a bad thing?

Being diagnosed with atypical CF can completely change a person's life, as it ends a long journey of uncertainty. Once a person with atypical CF starts to receive appropriate care, they may report a tremendous improvement in their well-being.

Studies have shown that, as a group, people with atypical CF enjoy better condition than people with classical Cystic Fibrosis. For example, most patients with atypical CF do not need to take pancreatic enzymes with their meals. However, although the overall outlook is better, individuals with atypical CF can experience quite severe disease, in particular lung infection, and it is important that they are monitored carefully. It is also important that CF teams appropriately segregate people with atypical CF to ensure that they are not exposed to bugs that can infect their airways. If good segregation policies are not in place, it could be argued that attending a standard CF clinic places someone with atypical CF at increased risk, which may outweigh the benefit of attending a CF clinic.

At what age can a person be diagnosed with atypical CF?

On the whole, people with atypical CF are diagnosed later than those with classical Cystic Fibrosis. Sometimes this can be in their adult life. The diagnosis of a lifelong condition can be upsetting for older children and adults and CF teams need to be empathetic to the needs of these patients.

Does the newborn screening programme identify infants with atypical CF?

The recent national programme to screen newborn infants for Cystic Fibrosis has been a tremendous success, however one of the results of this programme has been the identification of a small number of infants with an unclear diagnosis. In Europe, this is called an equivocal diagnosis of Cystic Fibrosis. These children are well and it is difficult to predict how they will progress over time. In North America, infants with an unclear diagnosis after newborn screening (NBS) have been given the term CFTR-related metabolic syndrome (CRMS). By using this

"It is likely that diagnoses of atypical CF will increase over the next five to ten years."

term the families are able to access the US medical system. This term has not been adopted in Europe and we will continue to monitor the progress of these children with an equivocal diagnosis following newborn screening carefully in clinics. With both newborn screening and the increased recognition of atypical CF by physicians looking after adult patients, it is likely that the number of patients with this diagnosis will increase over the next five to ten years.

Should patients with atypical CF carry out normal CF treatment regimens?

The basic principles of CF care – maintaining excellent weight, keeping the airways free of infection and encouraging a healthy and active lifestyle – apply to patients with atypical Cystic Fibrosis. It is important that CF teams have systems in place to achieve these goals; however, it may be that someone with atypical CF who has excellent weight and health does not need to be seen as frequently as someone with classical Cystic Fibrosis. If that is the case they (or their carers) must have a clear idea of signs or symptoms that they should be aware of and they should be able to contact the CF team easily for advice.

“Once a person with atypical CF starts to receive appropriate care, they may report a tremendous improvement in their well-being.”

In summary

Some people have signs and symptoms consistent with CF but do not fulfill the strict rules to make a diagnosis of Cystic Fibrosis. Many physicians use the term atypical CF to describe these people. A diagnosis of atypical CF can help someone access appropriate care and this can have a tremendous impact on their well-being. On the whole, people with atypical Cystic Fibrosis have less severe condition than people with classical CF, however individuals can be significantly affected and CF teams must have appropriate systems in place to provide these people with the monitoring and care they require.

Dr Kevin W Southern, Reader and Honorary Consultant in Paediatric Respiratory Medicine, University of Liverpool

“The consultant couldn’t really say what the future held.”

Elaine Mallion, who turns 50 this month, was diagnosed with atypical CF in her thirties.

I’d been seeking an explanation for a fairly persistent, clear-the-throat sort of cough, without any joy. At least my husband always knew where to find me in a supermarket! Then in 1993 when I was 31, I had a chest infection, which took about six weeks to shake off. After various referrals, I was diagnosed as having atypical Cystic Fibrosis. As mine is apparently a rare mutation the consultant couldn’t really say what the future held, as there were so few statistics on this form of Cystic Fibrosis. *“You’ll probably be much the same for five years or so, after that we don’t really know...”*

I’d been living with the cough since childhood. When I was about 16, I was referred to an ENT consultant who thought it may be something to do with my sinuses. When I left home and started to talk to GPs myself, I was referred for acupuncture and allergy

tests (some intolerance to dairy products was identified) and I was prescribed inhalers and nasal sprays for possible asthma and allergic rhinitis.

I think, after all those years, it was a relief to know there was some actual reason for my cough. But CF? That was a bit of a shock. All I knew about Cystic Fibrosis at that stage is that people were generally lucky if they survived into their thirties. There was no history of it in my family. My husband and I had just reached the stage where we were thinking of having children. After the diagnosis, we decided not to start a family, mainly because we really didn’t know what the prognosis was and how having children would affect my health. Seventeen years on, I wonder if it was the right decision (hindsight is a wonderful thing).

Once I’d had the diagnosis I decided to take steps to make sure I kept my lungs fit. As one of my friends once said: *“It’s good that you’ve got something that encourages you to go to the gym!”* I also enjoy cycling.

Given that I’ve got CF, I actually feel incredibly lucky. This month, I’ll be celebrating my 50th birthday. So far (touch wood), only my lungs seem to have been affected and even then, they’re fine most of the time. I take oral antibiotics and do some daily physio with the Flutter device. Of course there are some difficulties, such as trying to get a decent price for travel insurance and sometimes GPs seem



Elaine Mallion

to find it hard to appreciate there are different forms of Cystic Fibrosis. I have also recently stopped working full time, as having been employed in a rather stressful position, I felt it was important to put my health first – I am currently doing voluntary work whilst exploring other options. But overall, I feel that I live my life much as any ‘normal’ person and hope to keep on doing so for some time to come!

Peer review of CF services – where are we now?

The project to improve and streamline the peer review process for CF services is progressing well and has now completed its initial consultation period. We have had an excellent response from patients, parents and clinicians who have completed questionnaires or taken part in events and teleconferences.

Our team of Expert Patient Advisers (EPAs) have been central to canvassing opinions, and EPA for the South West Sophie Lewis and I have compiled a report which will appear on the CF Trust website in due course. A big thank you to all of you who got in touch to share your ideas, and contribute to this important piece of work. The next phase of the project will be



Peer reviews help CF Centres and Clinics improve the care they are able to offer patients

starting this autumn with two pilot peer reviews, testing out a new process and handbook which will contain everything we need to know in order to deliver an efficient and effective service review. It will have information for staff in the NHS, managers, commissioners, parents/patients and our staff here at the CF Trust who will continue to facilitate the reviews.

Future reviews will be focused around the revised Standards of Care 2011 (an updated version of the widely-used CF Trust Standards originally produced in 2001),

“Up until the end of 2009 peer review had helped to lever an additional £18million of NHS funding for CF care that would not have otherwise been forthcoming.”

which are currently being developed by leading CF clinical experts from all professions across the UK.

Since the Cystic Fibrosis Trust first implemented the process of peer review in 2006, and having now completed the first round of reviews for all CF specialist services, peer review continues to be seen as a vital tool in assessing services against the UK Standards of Care by NHS managers and CF clinical teams. Up until the end of 2009 peer review had helped to lever an additional £18million of NHS funding for CF care that would not have otherwise been forthcoming. It is clearly important, given the current economic climate and the continual squeezing of NHS budgets, that we continue this process to ensure that all people living with CF in the UK have fair and equal access to the very best possible quality of treatment and care.

Alicia Ridoult, Clinical Care and Commissioning Manager, Cystic Fibrosis Trust

New CF Trust publication provides support for physiotherapists

In July, the Cystic Fibrosis Trust published a revised version of its physiotherapy consensus document, entitled *Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis*.

The document, which provides detailed guidance on issues such as airway clearance techniques, exercise and inhalation therapy, was produced by a working group of specialist CF physiotherapists from across the UK.

Penny Agent, Specialist CF Physiotherapist at the Royal Brompton Hospital in London and chair of the working group said: “This comprehensive document of good clinical practice will be a useful tool to all physiotherapists and other clinicians involved in the delivery of care to people with CF, and as well as highlighting expert practice it is intended to encourage physiotherapists to local guidance tailored to their individual needs.”

Cystic Fibrosis Trust consensus documents provide detailed guidance about key issues in Cystic Fibrosis for those involved in CF care, treatment and research. Each document is produced by a specialist working group and feedback sought from the wider CF clinical community and other experts, and by CF patients and parents in order to reach a consensus on best practice in the areas covered. Our consensus



A new CF Trust consensus document will help improve CF physiotherapy services across the UK

documents can be downloaded at www.cftrust.org.uk/aboutcf/publications or printed copies ordered by contacting the CF Trust.

UK Cystic Fibrosis Registry update

The annual UK Cystic Fibrosis Patient Registry Report for 2009 was published on the Cystic Fibrosis Trust website in March this year. For the first time, data for each CF Centre and Clinic was identifiable, meaning that it is now possible to compare the clinical outcomes for the service that you attend with other services in the UK. We do feel that the current report format is rather heavy going in terms of the amount of statistical data with only brief explanations of some of the findings; therefore we are currently reviewing how the report may be presented in future, perhaps producing more than one version to account for the different audiences. If you have viewed the report we hope that you found it useful and interesting and, indeed, we would value any feedback.

The 2010 Registry Report is due to be published on our website by the end of this year. We are really pleased to see a continuing increase in the number of patients registered on the database, as well as an increase in the number of patients for whom there is full data, based on clinical information from their Annual Review. This information is very important in

“Data from the CF Registry helps researchers develop new and improved CF treatments.”

helping us to understand how patients are doing over a period of time in terms of their clinical outcomes. The clinical data also helps researchers to develop new and improved treatments, and it now ensures that CF services are funded in accordance

with the level of treatment and care required for each individual patient.

We hope that like us you will be encouraged by the increasing quality and quantity of data supplied by each service, and provided by individuals, and by the openness that we achieved in being able to identify every service with the aim of

driving up standards of care across the whole of the UK.

Jo Osmond, Director of Clinical Care and Commissioning, Cystic Fibrosis Trust.

The 2009 Registry Report can be viewed at: www.cftrust.org.uk/research/applydata

If you would like to comment on the report, please email publications@cftrust.org.uk.

Leaving a legacy: Are you worth more than you think?

In January 2011 we published an article in *CF Today* to answer some of your questions about making and changing wills. While you plan for the future, obtaining professional advice and having your will carefully drafted can also help with Inheritance Tax planning. You may not be aware that donations made to charity are tax exempt and free of Inheritance Tax and can therefore help to reduce your tax bill.

Inheritance Tax – how it might affect you

Inheritance Tax is paid on an estate when somebody dies. It's also sometimes payable on trusts or gifts made during someone's lifetime. Many estates don't have to pay Inheritance Tax because they're valued at less than the threshold set by HM Revenue & Customs – currently £325,000 for individuals and £650,000 for married couples. This may seem like a large sum of money, but if you include your home, you may find your savings and possessions add up to more than that. Inheritance Tax is charged at 40% on the amount over the threshold.

Changes on the way

“I want to make giving 10% of your legacy to charity the new norm in our country,” the Chancellor George Osborne announced in his March budget. The Government will reduce the rate of Inheritance Tax by 4% in cases where at least 10% of the total value of an estate is donated to charity. This is due to come into effect on 6 April 2012. The Treasury has launched a consultation about the relief and how it will be implemented and we will keep you updated when more details are available.

Why legacy income is so important

Last year we received just under £1million in legacy income.

This amount could enable the Cystic Fibrosis Trust to provide information, advice and support to people affected by Cystic

“Donations made to charity are tax exempt and free of Inheritance Tax and can therefore help to reduce your tax bill.”



Legacy income helps us to improve the lives of people with living with CF

Fibrosis for an entire year. This includes our publications, grants such as pre-payment certificates for prescription charges and travel expenses for transplant assessments, and the costs of running our helpline.

This amount could almost cover our clinical care programme for a year, which aims to ensure the clinical care for people with CF is as good as it can be, wherever they live in the UK. This includes our programme of peer reviewing CF clinics (see page 14) and actively supporting clinicians around the UK and their teams to provide the best possible care.

Legacy income enables us to continue with our vital work, helping to improve the quality and length of life for people with Cystic Fibrosis. To find out more about leaving a gift in your will to the CF Trust, please contact Sue Whitehead, Legacy Marketing Manager at swhitehead@cftrust.org.uk or 020 8290 8051.

Founded in 1964, the Cystic Fibrosis Trust is the UK's only national charity dealing with all aspects of Cystic Fibrosis.

Our objectives are to:

- Fund medical and scientific research to develop a cure and provide effective treatments for Cystic Fibrosis.
- Ensure appropriate clinical care for those with Cystic Fibrosis.
- Provide information, advice, support and, where appropriate, financial assistance to anyone affected by Cystic Fibrosis.

Cystic Fibrosis Trust

11 London Road, Bromley, Kent BR1 1BY

Tel: 020 8464 7211 Fax: 020 8313 0472

www.cftrust.org.uk

You can view *CF Today* online and download our extensive range of factsheets and booklets providing further information about Cystic Fibrosis at

www.cftrust.org.uk/aboutcf/publications



Cystic Fibrosis Trust Helplines

Our Support Service has three Helplines offering the following services:

For information and advice about benefits and how to apply for them –



Benefits Advice
0300 373 1010

For a *confidential* service that enables anyone to obtain information, advice and support on any aspect of Cystic Fibrosis –



CF Helpline
0300 373 1000

For information and advice on how to access small grants from the Cystic Fibrosis Trust and other organisations –



Welfare Grants
0300 373 1020

Our Helplines operate from 9am – 5pm weekdays. An answer machine is available during busy periods and outside these hours.

You can also access our website www.cftrust.org.uk to find out more about CF Trust Helplines and to download various forms and factsheets relating to these services.