

CF STORM

CLEARING THE AIR

A randomised open label trial to assess change in respiratory function for people with cystic fibrosis (CF) established on triple combination therapy (Kaftrio™) after rationalisation of nebulised mucoactive therapies

Establishing a collaborative approach

The study was led by Gwyneth Davies and Kevin Southern, two doctors with experience in CF and research. The study represented a collaboration between the Cystic Fibrosis community (including patients and their families), the UK Cystic Fibrosis Trust, Universities, Clinicians and CF team members. It was designed to address the number one research priority identified through the James Lind Alliance Priority Setting Partnership for CF published in 2018. The trial was funded by the UK government and supported by the CF Trust's Clinical Trials Accelerator Platform (CTAP). CTAP is a UK-wide network including dedicated trial coordinators, enabling clinical trial participation for more people with CF across the UK.

Influence of Lived Expertise in study design

The concept of CF STORM was initiated in 2019 in direct response to research priorities set by people with lived experience of CF and their healthcare teams. The number one priority was "What are the effective ways of simplifying the treatment burden of people with cystic fibrosis?". The demand to identify ways to "reduce treatment burden" accelerated with the emergence of new effective treatments called modulator therapies. CF STORM enrolled people with CF established on a modulator called elexacaftor-tezacaftor-ivacaftor (short name, Kaftrio™).

The study name was created with community members and stands for CF Streamlining Treatments Or Reducing Medications (CF STORM).

People with CF and their families expressed their preferences for what medications to look at, what to measure and how, determining what information would give the reassurance they wanted going forward. They identified daily nebulised therapies as the most burdensome of their daily treatments with a focus on treatments which support clearance of airway secretions, called mucoactive treatments (dornase alfa and

hypertonic saline). This was in preference to other common daily therapies such as nebulised antibiotics.

The community also determined that the respiratory function measure of FEV₁ (which stands for “Forced Expiratory Volume in One Second”) was the most reliable measure and one that people with CF are familiar with. Lived expertise helped make sure CF STORM would fit in with usual CF care, rather than needing extra study appointments. This was essential for a study addressing treatment burden. People with lived experience continued to contribute to many other aspects of study delivery, including recruitment strategies, data collection and ongoing communications, through membership on the Trial Management Group and the Oversight Committees.

Where was the study undertaken?

Forty paediatric and adult CF centres identified and approached participants to be in the study. These sites were across the UK, and the inclusive nature of CF STORM enabled people with CF who didn’t usually have opportunity to contribute to research to be involved. Recruitment to the study began in July 2021 and finished in August 2024. Participants were followed for 12 months, with study data collected from routine clinic visits and online questionnaires, making this a relatively easy study for participants to take part in.

Why was this research needed?

CF STORM was designed to provide confidence for people taking Kaftrio™, that they might be able to stop their daily mucoactive nebulised therapies without affecting lung health. The aim was for the results to support conversations about long term treatments between people with CF and their care teams.

It is important for people with CF and their families to have clear evidence on which to base decisions with respect to their treatment choices. The study provided a supportive environment to try. Some people on Kaftrio™ had already made a decision to stop nebulised mucoactive treatments prior to the study. These people could not participate.

What was the main question studied?

“Can people with CF on Kaftrio™ treatment, discontinue their mucoactive nebulised therapies without a large fall in their respiratory function?”

Who participated in the study?

591 children and adults with CF were recruited to the study across the UK. Children needed to be six years or over and able to do spirometry reliably (the respiratory function

test). Participants also needed to have stable condition and an FEV₁ above 40% of what would be predicted for them.

What happened to the participants during the study?

All participants were randomly allocated to either stop or continue their nebulised mucoactive treatments. Participants were followed for twelve months. Usual clinic visits were recorded on the CF Registry, a large national database which already collected health information from over 99% of people with CF in the UK. The information recorded includes treatments, lung function, hospital admissions and quality of life.

As well as the main study outcome (change in respiratory function, measured by FEV₁), the study collected a number of other important outcomes, such as number of courses of antibiotics prescribed and number of pulmonary exacerbations (a chest infection associated with worsening of symptoms and/or lung function). All exacerbations recorded on the registry were included in our results, irrespective of treatment or type of treatment. Participants were also sent questionnaires by email, asking about their quality of life and the impact of being on the study.

People taking part completed the 12-month study and had information about their lung function and health recorded on the CF Registry. We didn't receive information from all people taking part at the time intervals we were expecting, due to timing of clinic visits. Some patients had these measures done outside of a specified time period, but we were able to include these results in a secondary analysis as they were still recorded on the CF Registry. Some patients self-reported or were recorded on the CF Registry as not continuing with their treatment allocation, for example if they were asked to stop and then restarted their mucoactive nebulisers by their clinical teams. We included these participants in the analysis of the most important outcome (change in FEV₁ over the 12 months).

What were the results of the study?

Both the 'stop' and 'continue' groups had minimal change in their lung function over the twelve months.

In younger children (6-11 years), there was a suggestion that stopping nebulisers might result in better lung function.

Over the 12 months, this large group of participants were stable with little need for extra treatments or hospital admissions. The group that stopped their nebulisers had slightly more antibiotics prescribed and reported more chest exacerbations. Overall, these differences were small and not found in other outcomes, such as need for intravenous antibiotic treatment. People stopping their nebulised treatments in the lower lung function group (which we defined as 40-69% of predicted lung function) were more likely to have a chest exacerbation than those continuing their nebulisers.

How has this study helped people with CF and their families

These results show that, for people with CF who are established on Kaftrio™, stopping nebulised mucoactive therapies is unlikely to result in a reduction in their lung function over twelve months. This result provides reassurance. However, the results also showed that it may also be more likely for people to need antibiotics if they stop nebulised mucoactive therapies, particularly in those with lower lung function. This was not the main question the study was trying to answer and needs further study but will be important as people consider their long-term treatments.

The results give people with CF and their families information that can support them in joint decision making with their CF team about their treatments. They will help people with CF and their families balance overall health and treatment burden. It is important that any changes to treatments are discussed with healthcare professionals and monitored carefully.

Details of any further research planned

These data will help support decision making between people with CF and their clinical teams. However, there are still questions remaining and further research is needed. This research might include more people with the lowest lung function group as included in CF STORM (40-69% predicted FEV₁), and also those with an FEV₁ below this too.

There is also a need to better understand the role of other therapies (including nebulised antibiotics) in people with CF on modulators such as Kaftrio™, and over a time period longer than 12 months.

Finally, it is important we better determine the impact of stopping therapies on the lived experience of people with CF and their families. CF STORM gave us some insight into this, but more studies are needed.

Where can I learn more about the study

The results of CF STORM will be published in a scientific journal. If you would like to find out more about the trial and the publications, then please visit the trial website: <https://www.cfstorm.org.uk>

The CF STORM team are also working with the UK Cystic Fibrosis Trust on a number of public facing events to announce the results to people with CF and their families and discuss the implications.