An intervention to support adherence to inhaled medication in adults with cystic fibrosis: the ACtiF research programme including RCT

Martin J Wildman,[1,2] Alicia O'Cathain,[2*]
Daniel Hind,[3] Chin Maguire,[3] Madelynne A Arden,[4]
Marlene Hutchings,[1] Judy Bradley,[5] Stephen J Walters,[2]
Pauline Whelan,[6] John Ainsworth,[6] Paul Tappenden,[2]
Iain Buchan,[6,7] Rachel Elliott,[8] Jon Nicholl,[2]
Stuart Elborn,[5] Susan Michie,[9] Laura Mandefield,[2]
Laura Sutton,[2] Zhe Hui Hoo,[1,2] Sarah J Drabble,[2]
Elizabeth Lumley,[2] Daniel Beever,[3] Aline Navega Biz,[2]
Anne Scott,[3] Simon Waterhouse,[3] Louisa Robinson,[3]
Mónica Hernández Alava[2] and Alessandro Sasso[2]

[1]Sheffield Adult Cystic Fibrosis Centre, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[2]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[3]Clinical Trials Research Unit, University of Sheffield, Sheffield, UK
[4]Centre for Behavioural Science and Applied Psychology, Sheffield Hallam University, Sheffield, UK
[5]Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK
[6]Health eResearch Centre, Division of Imaging, Informatics and Data Sciences, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
[7]Department of Public Health and Policy, Institute of Population Health Sciences, University of Liverpool, Liverpool, UK
[8]Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[9]Centre for Behaviour Change, University College London, London, UK

*Corresponding author a.ocathain@sheffield.ac.uk

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Scientific summary

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Scientific summary

Background

The World Health Organization states that poor adherence to medication is a worldwide problem associated with poor health outcomes and increased costs to health-care systems. This is particularly problematic in chronic conditions including cystic fibrosis. Existing nebulised therapies for cystic fibrosis are effective but only when adherence levels are high. Low levels of adherence are associated with poor health outcomes, including increased rates of pulmonary exacerbations and rapid lung function decline. Objectively measured adherence levels in cystic fibrosis are estimated to be as low as 30–40%, as measured on dose-counting nebulisers. Subjective estimates of adherence levels are higher, at around 80%.

To date, behaviour change interventions designed to increase adherence in cystic fibrosis have demonstrated little success. This may be because interventions have not targeted the most appropriate factors, because there is a lack of studies using a theory- and evidence-based approach to intervention development and because interventions tend to assume that one size fits all, despite evidence that the factors affecting adherence may be person-specific. Indirect or subjective measures of adherence have also limited the reliability of adherence measurements in these studies.

This programme aimed to develop a theory- and evidence-based intervention that targets specific capability, opportunity and motivational issues faced by people with cystic fibrosis, to support people with cystic fibrosis to increase adherence to nebulised medications and, through that, to reduce the number of exacerbations that they experience.

Objectives

The aim was to develop and evaluate an intervention to support adherence to inhaled medications for people with cystic fibrosis.

Our specific objectives map to three work packages:

1. to develop a mechanism for objective measurement of adherence through (1) development of a data capture and transfer infrastructure that can collect time- and date-stamped data and (2) display this data both on a 'CFHealthHub' website, for use by people with cystic fibrosis and their clinicians, and on a CFHealthHub mobile application, for people with cystic fibrosis, and (3) develop the CFHealthHub web interface with patients and clinicians
2. to develop an evidence-based behaviour change intervention to increase adherence to nebulised cystic fibrosis medications that works concurrently with the CFHealthHub digital platform
3. to evaluate the CFHealthHub intervention (platform plus behaviour change intervention) in terms of (1) clinical effectiveness, (2) acceptability and (3) cost-effectiveness and to examine the processes that drive these outcomes.

Methods and results

Work package 1

Developing the technology and infrastructure to collect adherence data

A data capture and transfer infrastructure was constructed that collected time- and date-stamped nebuliser utilisation data from chipped nebulisers and displayed these data on a CFHealthHub website for use by both people with cystic fibrosis and their clinicians. A mobile application was developed to display data for use by people with cystic fibrosis. Agile software development methods were used to develop the CFHealthHub website and application. Sprint cycles were released, iteratively incorporating technical requirements identified by the research team and the nebuliser supplier. This continued throughout the feasibility study (work package 3.1). Decisions on which changes to implement were made by the research team, in consultation with the patient and public involvement panel.

Website and mobile application iterations were conducted over 18 months. The priority was to display to people with cystic fibrosis and their care team objective adherence data captured from dose-counting nebulisers. Technical architecture was developed to enable this, along with role-based interfaces for clinicians/interventionists, members of the research team and people with cystic fibrosis. Alongside adherence data display, the following behaviour change intervention website features were developed and integrated: 'My Education' and 'Problem-solving', 'My Toolkit', a screening tool to support intervention tailoring, peer videos, 'Action Planning', 'Coping Planning', 'Party Planning', 'Day Planning', push notifications, click and touch analytics, and export functionality. The final version of the platform was completed for the launch of the full-scale randomised controlled trial.

Work package 2

Understanding the illness perceptions and treatment beliefs of people with cystic fibrosis (work package 2.1A)

Eighteen face-to-face semistructured qualitative interviews were conducted with people with cystic fibrosis in one UK cystic fibrosis centre to explore perceptions of their condition, their treatments, the acceptability of visual displays of their recent medications adherence, and perceived barriers to and facilitators of adherence to their treatments. The perceived barriers to and facilitators of adherence to treatments were interpreted using the theoretical domains framework. Key contextual issues related to desires to feel normal, varying levels of openness about their condition, health beliefs, treatment burden, tiredness and emotions. Specific barriers to and facilitators of medication adherence covered all 14 theoretical domains. Ways of improving the acceptability of adherence graphs were identified. Findings fed into the intervention development in work package 2.2.

Patient story video interviews to develop the CFHealthHub intervention (work package 2.1C)

A purposive sample of 14 people with cystic fibrosis with high levels of adherence (> 80%) or sustained increases in adherence level were interviewed face to face to identify positive experiences of overcoming barriers to adherence. Interviews were video-recorded and extracts selected. A series of 'talking heads' video clips were integrated into the behaviour change intervention as a resource on the CFHealthHub platform (work package 2.2).

Behaviour change intervention development (work package 2.2)

A four-stage process to plan, design, create and refine the behaviour change intervention was conducted. A mixed-methods approach, combining theory and evidence in the capability, opportunity, motivation – behaviour model and behaviour change wheel and the 'person-based approach', was used to iteratively develop the behaviour change intervention part of the intervention, alongside the development of the digital platform. This incorporated findings from work package 1, work package 2.1A, work package 2.1C and the feasibility study in work package 3.1 as well as two additional

studies: (1) an early prototype of the intervention was tested on five people with cystic fibrosis, who were interviewed after 1 week and 1 month, and (2) 22 participants received four intervention sessions from a physiotherapist/interventionist and were given access to CFHealthHub over five iterative cycles of development. Participants were interviewed and six undertook 'think aloud' interviews, which were recorded, during use of the CFHealthHub website. Changes to the intervention were considered based on the feedback, and refinements were made for each new iteration of the intervention.

An intervention manual and training programme for interventionists was produced and used in the feasibility study (work package 3.1). The training programme comprised face-to-face and online elements and included assessments of competence. Further amendments were made to the intervention and the training programme in response to findings from the feasibility study process evaluation before use in the full-scale randomised controlled trial (work package 3.2).

Work package 3

Feasibility study (work package 3.1)

A pilot open-label, parallel-group randomised controlled trial with concurrent mixed-methods process evaluation was conducted. Interventionists were recruited in two UK cystic fibrosis centres. Participants, recruited at both centres, were people aged ≥ 16 years with cystic fibrosis, on the cystic fibrosis registry, not post lung transplant or on the active transplant list, who were able to consent and not using dry-powder inhalers. They were given a nebuliser with time- and date-stamped inhalation data transfer capability and randomised on a 1 : 1 allocation. Intervention arm participants received the behaviour change intervention with access to CFHealthHub platform; control arm participants received usual care. Feasibility was determined on recruitment of > 48 participants (75% of target) in 4 months, valid exacerbation data available for > 85% of those randomised, change in per cent adherence (a secondary outcome for the full-scale randomised controlled trial), and positive perceptions of the intervention from qualitative interviews with intervention ($n = 14$) and control ($n = 5$) participants, interventionists ($n = 3$) and multidisciplinary team members ($n = 5$). Recruitment ($n = 64$) and retention (94%) targets were met. Five serious adverse events (not related to the intervention) were identified. At study completion, mean change in adherence was 10% (95% confidence interval −5.2% to 25.2%).

In the qualitative interview study there was evidence of the expected behaviour change mechanisms of action and mechanisms of action associated with effective telehealth interventions for self-management support: relationships, visibility and fit. The intervention was tailored to individuals but there were challenges in how the intervention fitted into some patients' busy lives when delivered through a desktop computer. Interventionists identified that patients with moderate adherence rates were more likely to benefit.

The feasibility study led to 25 key changes to randomised controlled trial procedures and the intervention. These included a longer recruitment accrual window, development of an application for mobile telephones, changes to the interventionist training and manual to emphasise 'active ingredients', and increased numbers of protocolised intervention review sessions.

Full-scale randomised controlled trial (work package 3.2) and process evaluation (work packages 3.3 and 3.4)

A full-scale, open-label, parallel-group randomised controlled trial with concurrent mixed-methods process evaluation to examine the clinical effectiveness of the final CFHealthHub intervention.
The intervention was delivered by physiotherapists in 13 out of the 19 centres and nurses, psychologists, a pharmacist and a dietitian in other centres. Some centres had two interventionists that shared the role, sometimes from different clinical disciplines.

Work package 3.2

People with cystic fibrosis from 19 UK cystic fibrosis centres, aged ≥ 16 years, on the cystic fibrosis registry and not post lung transplant or on the active transplant list, who were able to consent and not using dry-powder inhalers, were given a nebuliser with time- and date-stamped inhalation data transfer capability. Participants were randomised on a 1 : 1 allocation to the intervention ($n = 305$) or usual care ($n = 303$). One participant randomised to the intervention arm withdrew on the day of consent, prior to baseline data collection. The primary outcome was adjusted incidence rate ratio of pulmonary exacerbations meeting the modified Fuchs criteria over a 12-month follow-up period. Key secondary outcomes were adjusted between-group differences in medication adherence, forced expiratory volume in 1 second (per cent) predicted and body mass index at 12 months. The adjusted incidence rate ratio of exacerbations at 12 months was 0.96 (95% confidence interval 0.83 to 1.12; $p = 0.638$). The adjusted mean difference in normative adherence was 9.5% (95% confidence interval 8.6% to 10.4%; $p < 0.001$) across 1 year, favouring the intervention. The adjusted mean difference in forced expiratory volume in 1 second (per cent) predicted was 1.4% (95% confidence interval −0.2% to 3.0%; $p = 0.082$) at 1 year, favouring the intervention. There was an adjusted mean difference in body mass index of 0.3 kg/m^2 (95% confidence interval 0.1 to 0.6 kg/m^2; $p = 0.008$), favouring the intervention.

Work package 3.3

The process evaluation consisted of (1) a fidelity study (including analysis of click analytics in CFHealthHub), (2) a survey of usual care consisting of an 11-item questionnaire completed by staff at each randomised controlled trial site at baseline ($n = 20$) and follow-up ($n = 19$), (3) a survey of user-perceived helpfulness of different intervention components at 12 months completed by 257 out of 305 intervention arm participants, (4) a qualitative study of interviews with 22 intervention users, 26 interventionists recruited to deliver the intervention in the randomised controlled trial and five members of the multidisciplinary team in five sites, (5) a mediation analysis to assess the mechanisms of action of the intervention and (6) trial monitoring data. Triangulation of the process evaluation components identified the following key findings:

- interventionist fidelity to the intervention was high at 18 out of 19 randomised controlled trial sites
- the intervention was substantially different from usual care because, although usual care varied between randomised controlled trial sites, access to objective adherence measurements was described as infrequent and ad hoc
- the intervention was acceptable to people with cystic fibrosis – all components were rated as mostly helpful, with first intervention sessions, adherence graphs/tables and face-to-face intervention sessions rated among the most helpful components
- some people with cystic fibrosis did not like the patient stories (videos) or setting formal action plans
- participants engaged with the intervention, including the tailored education and problem-solving, and personalised target setting and rewards
- the mean adherence between 6 and 12 months was primarily mediated by awareness of medication usage (overall, 37% of the total effect mediated, 95% confidence interval 24% to 51%), with habit formation (9% of the total effect mediated, 95% confidence interval 3% to 16%) the second most important factor.

The qualitative research identified additional mechanisms of action, including how interventionists spending time with people with cystic fibrosis and listening to wider life concerns could help to build relationships and trust that facilitated adherence improvement, and how changes occurred if the intervention was delivered at the right time in patients' lives. People with cystic fibrosis with different baseline adherence rates responded differently to the intervention. Context varied between randomised controlled trial sites in terms of the engagement of the multidisciplinary team with the intervention and the strengths of the interventionists in each site.

Health economic analysis (work package 3.5)

We undertook two related economic analyses to assess the cost-effectiveness of the intervention: (1) a short-term within-trial economic evaluation that compared health gains and costs for the intervention and usual care arms using patient-level data from the 1 year primary outcome window of the randomised controlled trial and (2) a model-based analysis that compared the intervention versus usual care over a lifetime horizon using multiple sources of evidence. The base case results for the within-trial analysis (including multiple imputation of missing data) indicated that the intervention generated 0.01 additional quality-adjusted life-years at an additional cost of £865.91 per patient; the corresponding incremental cost-effectiveness ratio was £71,136 per quality-adjusted life-year gained. The health economic model suggested that the intervention could generate 0.17 additional quality-adjusted life-years and cost savings of £1790 compared with usual care; this assumes a lifetime horizon and that the treatment effect lasts for 10 years. Therefore, the adherence intervention is expected to dominate usual care. Sensitivity analyses indicated that the conclusions of the economic analysis were sensitive to assumptions regarding (1) the duration over which health effects and costs of the adherence intervention apply, (2) the impact of the intervention on the patient's forced expiratory volume in 1 second (per cent) predicted and (3) increases in adherence to nebulised treatments and associated impacts on drug-prescribing levels.

Conclusions

Summary of findings

The CFHealthHub was successfully developed. In the full-scale randomised controlled trial there was no statistically significant reduction in the primary outcome of the number of pulmonary exacerbations at 12 months. Clinically and statistically significant improvements in the key secondary outcome of normative adherence were observed. The magnitude of the increase in adherence, at 10% on average, may not have been large enough to affect exacerbations. The intervention was delivered with fidelity, and key mechanisms of action, including self-monitoring, were observed. The health economic model suggested that the intervention is expected to generate additional health gains of 0.17 quality-adjusted life-years and cost-savings of £1790 over the patient's remaining lifetime. This finding is dependent on assumptions regarding the duration over which costs and effects of the intervention apply, the impact of the intervention on forced expiratory volume in 1 second (per cent) predicted and the relationship between increased adherence and drug-prescribing levels.

Limitations

Number of exacerbations is a sensitive and valid measure of clinical change used in many trials. However, data collection of this outcome in the context of this trial was challenging and could have been subject to bias. It was not possible to measure baseline adherence accurately. It was not possible to quantify the impact of the intervention on the number of packs of medicines prescribed. As a consequence, there remains uncertainty regarding the relationship between improving adherence on overall treatment costs incurred by the NHS.

Implications for practice

An infrastructure for measuring objective adherence data was established that could be used in routine care. The availability of these data may be useful for accurate diagnosis and medicines optimisation. The CFHealthHub intervention provided an effective method to support people to increase their adherence. Although subject to uncertainty, adopting the CFHealthHub intervention may produce small improvements in health for the NHS.

Recommendations for future research in priority order

- Given the non-significant difference in the primary outcome, further research is required to explore why an increase in objective normative adherence did not translate into reduced exacerbations, and to develop interventions that reduce exacerbations.
- The existing intervention could be adapted or tailored to address the needs of people with cystic fibrosis with different levels of baseline adherence, including those with low levels of baseline adherence who often have complex problems.

Trial registration

The trial was registered as follows with the NHS Research Ethics Committee, Health Research Authority and International Standard Randomised Controlled Trials Number registry:

- work package 2.1A – a study of the views of people with cystic fibrosis about their condition and treatments (Hampshire A Research Ethics Committee 14/SC/1455; Integrated Research Application System 171049).
- work package 2.1C – a study to produce videos for the CFHealthHub website (Camden and Kings Cross Research Ethics Committee 15/LO/0944; Integrated Research Application System 182367).
- work package 2.2B – a study to develop a behaviour change intervention to help people with cystic fibrosis manage treatment adherence (South Yorkshire Research Ethics Committee 15/YH/0332; Integrated Research Application System 184477).
- work package 2.2B(1) – a study to understand how to use the eTrack (PARI GmbH, Starnberg, Germany) nebuliser and Bi-neb nebuliser to help people with cystic fibrosis to manage their inhalation treatments (West of Scotland Research Ethics Committee 5 15/WS/0089; Integrated Research Application System 177900).
- work package 3.1 – a feasibility study comprising an external pilot randomised controlled trial and process evaluation (London Brent Research Ethics Committee 16/LO/0356; Integrated Research Application System 199775). Current Controlled Trials ISRCTN13076797.
- work packages 3.2 and 3.3 – a randomised controlled trial and parallel process evaluation to determine the efficacy of CFHealthHub and manuals and to conduct a parallel process evaluation (London Brent Research Ethics Committee 17/LO/0035; Integrated Research Application System 218519). Current Controlled Trials ISRCTN55504164.

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Editorial contact: journals.library@nihr.ac.uk

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