

Strength-Oriented Virtual Exercise Training Intervention in Children and Adolescents with Cystic Fibrosis Under CFTR Modulators (the FIQMODE Study): Study Protocol for a Randomized Controlled Trial

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Muscle health has not been thoroughly analyzed in pediatric cystic fibrosis (CF) under elxacaftor/tezacaftor/ivacaftor (ETI) therapy together with exercise interventions in randomized controlled trials (RCTs). The aim of this study will be to determine the effects of a virtual live exercise training intervention on muscle health and cardiorespiratory fitness (CRF) variables in a pediatric population with CF under ETI therapy. The 'FIQMODE' Study (FIQ for CF in Spanish, or *fibrosis quística*; MOD for modulator therapy; and E for exercise) is a two-arm RCT to evaluate the feasibility and efficacy of a novel exercise intervention to improve the muscle health and quality of life (QoL) of children and adolescents with CF under ETI pharmacological therapies. The exercise group will follow a 16-week, supervised, strength-oriented virtual live exercise training intervention. The control group will follow the standard World Health

Organization recommendations for physical activity. Primary outcomes will be muscle health (lower and upper limb strength, respiratory muscle strength, lower limb functional mobility, anthropometry, and body composition) and CRF. Secondary outcomes will be clinical history, lung function, inflammatory status, lifestyle and QoL, adherence, and the Mediterranean Diet Quality Index. Participants will complete measures at baseline (pre-intervention), 16 weeks post-intervention, and 8 months follow-up after the intervention. FIQMODE will provide an evidence-informed protocol for exercise-based therapy focused on outcomes reported in a robust RCT that can be applied across children and adolescents with CF under ETI therapy. FIQMODE will support the standardization of CF therapies with ETI together with exercise therapies, which will maximize the usability of exercise in medical applications, improve muscle quality, reduce pulmonary exacerbation, boost pharmacological improvement, and ultimately help improve the lifestyle of children and adolescents with CF.

Trial registration: The protocol has been approved by the Ethics Committee of the Universidad Politécnica de Madrid (REF. 20231215) and registered on ClinicalTrials.gov (NCT06322446). This research was funded by the Instituto de Salud Carlos III, which is co-funded by the European Regional Development Fund (PI 23/00299). The Instituto de Salud Carlos III supported this study through the project agreement “FIQMODE” with the Universidad Politécnica de Madrid (C2311600157). © 2025 The Author(s). Current Protocols published by Wiley Periodicals LLC.

Keywords: exercise • healthy lifestyle • lung diseases • muscle strength • physiology • respiratory function tests

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
ATS	American Thoracic Society
BF	respiratory frequency
BR	respiratory reserve
BFMI	body fat mass index
BMI	body mass index
CERT	Consensus on Exercise Reporting Template

CFLD	cystic fibrosis–associated liver disease
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFRD	cystic fibrosis–related diabetes mellitus
CFTR	cystic fibrosis transmembrane conductance regulator
CK	creatine kinase
CONSORT	CONsolidated Standards Of Reporting Trials
CO ₂	carbon dioxide
CPET	cardiopulmonary exercise test
CRF	cardiorespiratory fitness
CRP	C-reactive protein
CV	coefficient of variation
EDTA	ethylenediaminetetraacetic acid
ELLA	simplified ELISA
ELISA	enzyme-linked immunosorbent assay
ETI	elexacaftor/tezacaftor/ivacaftor
EQUATOR	Enhancing the QUALity and Transparency Of health Research
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 s
FFMI	fat-free mass index
FIQMODE	<i>Fibrosis Quística</i> , MODulator therapy, Exercise
FVC	forced vital capacity
HGS	handgrip strength
HHD	hand-held dynamometer
HIUNJ	Hospital Infantil Universitario Niño Jesús
HRQoL	health-related quality of life
HRyC	Hospital Universitario Ramón y Cajal
HULP	Hospital Universitario La Paz
IL-6, IL-8	interleukin 6, interleukin 8
ISAK	International Society for the Advancement of Kinanthropometry
KIDMED	Mediterranean Diet Quality Index
LDH	lactate dehydrogenase

LMM	linear mixed-effects model
MCID	minimum clinically important difference
MAR	missing at random
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
MPO	myeloperoxidase
O ₂	oxygen
OUES	oxygen pulse and oxygen uptake efficiency slope
PA	physical activity
PAQ-A	Physical Activity Questionnaire for Adolescents
PAQ-C	Physical Activity Questionnaire for Children
PERT	pancreatic enzyme replacement therapy
PET CO ₂	partial pressure of carbon dioxide
PET O ₂	partial pressure of oxygen
QoL	quality of life
REDCap	Research Electronic Data Capture
RER	respiratory quotient
RCT	randomized controlled trial
SD	standard deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SpO ₂	oxygen saturation
sTnl	serum troponin
STS	sit-to-stand test
TGF- β 1	transforming growth factor β 1
TNF- α	tumor necrosis factor α
TUG	Timed Up and Go
VASANA	Visual Analogue Scale of Adherence to Treatment
VE	ventilation
VE/VCO ₂	carbon dioxide equivalent
VE/VO ₂	oxygen equivalent
VO ₂ peak	maximum oxygen consumption
VT1	ventilatory threshold

INTRODUCTION

Cystic fibrosis (CF) is a multisystemic and autosomal recessive genetic disorder that affects around 90 in 100,000 individuals worldwide (Shteinberg et al., 2021). CF is currently one of the most prevalent rare diseases in children and adolescents (Bell et al., 2020). Since its first description in 1938 (Andersen, 1938), several diagnostic and therapeutic approaches have transformed CF from a pediatric fatal disease to a nonfatal disease with an estimated median survival time of nearly 61 years of age according to the Cystic Fibrosis Foundation's 2023 Patient Registry Annual Data Report (Marshall et al., 2023). CF is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein, identified in 1989 (Kerem et al., 1989; Riordan et al., 1989; Rommens et al., 1989). This protein functions as a channel that regulates chloride passage (and sodium and water as a consequence of chloride passage) within epithelial cells (Elborn, 2016). CFTR malfunction is responsible mainly for respiratory problems, pancreatic insufficiency, nutrient malabsorption, malnutrition, liver complications, and fertility issues, among other health effects (Bergeron & Cantin, 2019; Elborn, 2016; Kamal et al., 2018; Shteinberg et al., 2021; Singh & Schwarzenberg, 2017). Additionally, mutations in the gene can affect skeletal muscle, bone mass, immune and hematological cells, and endothelial cells (Divangahi et al., 2009; Khalaf et al., 2020; Lamhonwah et al., 2010; Plebani et al., 2017; Totani et al., 2017; Tousson et al., 1998). Although the prognosis, quality of life (QoL), and clinical characteristics of patients are mainly linked to the condition of the respiratory system, skeletal muscle weakness and atrophy are also relevant markers in individuals with CF (Anne-Sophie et al., 2024; Gruet et al., 2017; Nixon et al., 1992).

In recent times, the longer life expectancy of individuals with CF has resulted in a rise in the co-occurrence of specific comorbidities and age-related diseases (Perano et al., 2014) and a necessity to embrace innovative approaches for CF clinical management (Calella et al., 2018; Galluzzi & Kroemer, 2019; Perano et al., 2014). As a result, therapeutics and the understanding of CFTR function and its mutations have improved, facilitating the development of targeted therapies such as CFTR modulators (Shteinberg et al., 2021; Zemanick et al., 2016). These modulators are considered the present and future of drug therapy for individuals with CF and are associated with an increased life expectancy (Gohy et al., 2021). Since ivacaftor was approved by the Food and Drug Administration (FDA) in 2012, other drugs have been developed to correct the protein defect at different points, resulting in the triple CFTR modulator combination elexacaftor/tezacaftor/ivacaftor (ETI).

CFTR modulator therapies have revolutionized CF management, yet limitations include their high cost and uncertainty about long-term muscle health efficacy, prompting investigation into complementary strategies, such as exercise-based interventions. Goetz and Savant (2021) noted that the financial benefit of different CFTR modulators, administered individually or in combination, has not yet been fully confirmed, particularly due to their considerable and consistently high expense. Nonetheless, the therapeutic efficacy of these pharmacological interventions in addressing the pathophysiology of CF is well established (Goetz & Savant, 2021). However, given that the cost of this pharmacological treatment is high (Angelis et al., 2015), it is important to explore the pulmonary and extrapulmonary effects of CFTR modulators together with other interventions, such as exercise-based physical interventions, due to the previously observed positive improvements in exercise capacity (Philipsen et al., 2024) and CF symptoms (Garcia-Perez-de-Sevilla et al., 2022; Radtke et al., 2022; Thorel et al., 2022). Systematic reviews of exercise-based interventions have reported positive outcomes and emphasize the need

for reproducible exercise protocols, which are currently lacking in CF (Garcia-Perez-de-Sevilla et al., 2022; Radtke et al., 2022; Thorel et al., 2022). These observational studies have reported improvements in active children and adolescents with CF under CFTR modulators, but without in-depth evaluations that involve exercise as the main treatment. The present study will determine whether personalized strength-oriented exercise, combined with ETI therapy, might enhance muscle health, cardiovascular fitness, pulmonary function, and body composition in CF. Additionally, it will evaluate the integration of individualized exercise regimens for each child or adolescent with CF.

ETI therapies are designed to correct abnormal CFTR folding and increase channel ion conductance and is available to more than 85% of people with CF over the age of 2 (CIMA-AEMPS, 2020a). Studies have shown that this treatment has a significant impact on improving lung function and nutritional status, decreasing sweat chloride concentration, and reducing pulmonary exacerbations (Ejiofor et al., 2020; King et al., 2022; Nichols et al., 2022), but the direct effect on muscle mass has not yet been examined using randomized controlled trials (RCTs). Some observational studies point to an improvement in long-term exercise capacity in individuals undergoing ETI treatment (Anne-Sophie et al., 2024). However, studies of ETI therapies have shown that the clinically significant improvements of pulmonary function and nutritional status do not consistently lead to the restoration of muscle function and muscle mass when relying solely on pharmacological treatment. This limitation is particularly evident among individuals experiencing malnutrition or physical inactivity. Incorporating strength-oriented exercise interventions may offer a complementary and synergistic benefit alongside CFTR modulator therapy, thereby contributing to a more comprehensive therapeutic outcome. In particular, to date, there have been no RCTs to investigate the specific effect of strength-oriented exercise on muscle health in children and adolescents under ETI treatment.

Recent studies show that young people with CF have lower levels of physical activity than healthy young people without CF (Kinaupenne et al., 2024) and that exercise intolerance is a major barrier for many children and adolescents, who are often unable to participate with their peers due to the risk of cross-infection. However, although exercise tolerance may improve with ETI treatment (Stastna et al., 2024), the effects of therapy with CFTR modulators on improving exercise capacity and maximum oxygen consumption ($\text{VO}_{2\text{peak}}$) are currently unclear (Gruber et al., 2024). Therefore, there is an urgent need for interventions to promote physical activity and exercise in young individuals with CF under ETI treatment.

Exercise might also be crucial in individuals with CF because of its anti-inflammatory effects, as reflected by reductions in blood biomarkers such as C-reactive protein (CRP) and the cytokines interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor α (TNF- α), and transforming growth factor β 1 (TGF- β 1) (Bene et al., 2020). Interestingly, in other pulmonary diseases, other training strategies, such as aerobic intervallic exercise, strength exercise, and/or combined exercise, used as a safe and effective alternative, have been shown to be associated with a lower risk of airflow limitation, less respiratory intolerance, less systemic inflammation, and greater adherence (Donadio et al., 2022; Gruet et al., 2022; Radtke et al., 2022; Santana Sosa et al., 2012).

Individuals with CF should not exercise in a group due to the possibility of cross-infection. In addition to reducing the risk of cross-infections, which is a particularly relevant concern in patients with CF, telematic exercise programs enable children and adolescents living in rural or remote areas to access specialized interventions delivered from urban hospitals or reference centers. This approach promotes equity in healthcare by overcoming geographic and logistical barriers that would otherwise limit adherence and participation. Thus, technology and the use of virtual live exercise training

interventions can be an important ally in promoting adherence to exercise in young individuals with CF by allowing the intervention to be individually tailored and accessed from a computer screen, under the supervision of professionals in Physical Activity and Sport Sciences. Numerous studies conducted before the era of CFTR modulators and included in systematic reviews have mentioned the need for further research in this field to establish the most appropriate exercise for this population (Garcia-Perez-de-Sevilla et al., 2022; Radtke et al., 2022; Thorel et al., 2022). Besides, in the present era of CFTR modulators, new singular ETI drugs raise the need to re-evaluate exercise interventions to avoid possible muscle damage as muscle function improves in young individuals with CF. Young individuals with CF are the population of interest for the present study, given that early adjustments to good lifestyle habits, including those related to exercise and physical activity, may ensure long-term positive influence and adherence, impacting the QoL of individuals with CF over the course of their lifetime. In the present context of a continuous evolution of CF treatment using singular ETI drugs, it is a relevant and novel complementary therapy to include strength-oriented virtual live exercise training interventions in children and adolescents with CF under CFTR treatment.

Strength-oriented virtual live exercise training interventions may improve muscle health, cardiorespiratory fitness (CRF), pulmonary function, body composition, QoL, and biochemical status in children and adolescents with CF under ETI therapy. The clinical course and adherence to exercise may signify a positive QoL influence for children and adolescents who participate in the exercise intervention. Consequently, this study will aim to determine the effects of a strength-oriented virtual live exercise training intervention on 1) muscle health, 2) CRF, 3) clinical history, 4) lung function, 5) inflammation status, 6) lifestyle and QoL, 7) adherence, and 8) Mediterranean Diet Quality Index (KIDMED) in a group of children and adolescents with CF under ETI treatment. Muscle health will be measured using peripheral muscle strength and respiratory muscle strength tests. Subjects will be followed up 8 months post-intervention to track their clinical evolution and exercise adherence by evaluating all study variables.

MATERIALS AND METHODS

Study Design

The ‘FIQMODE’ Study (FIQ for CF in Spanish, or *fibrosis quística*; MOD for modulator therapy; and E for exercise) will be a two-arm RCT to evaluate the feasibility and efficacy of a novel exercise intervention to improve the 1) muscle health, 2) CRF, 3) clinical history, 4) lung function, 5) inflammation status, 6) lifestyle and QoL, 7) adherence, and 8) KIDMED of children and adolescents with CF under pharmacological ETI therapies. This study will have a 1:1 allocation ratio with a superiority framework between the exercise group and the control group.

The exercise group will follow a 16-week, supervised, strength-oriented virtual live exercise training intervention. The control group will follow the standard World Health Organization (WHO) recommendations for physical activity. In addition, a longitudinal follow-up will be included to assess the clinical evolution of both groups during the 8 months after the intervention to analyze adherence to treatment (Fig. 1). The flow diagram shown here follows the CONSORT (CONSolidated Standards Of Reporting Trials) guidelines for RCTs recommended by the EQUATOR (Enhancing the QUALity and Transparency Of health Research) network (Eaton, 2013).

Muscle health will be measured using upper and lower limb strength, lower limb functional capacity, and respiratory muscle strength by means of dynamometry, number of sit-to-stand repetitions, and maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), respectively. CRF will be measured by means of ergospirometry.

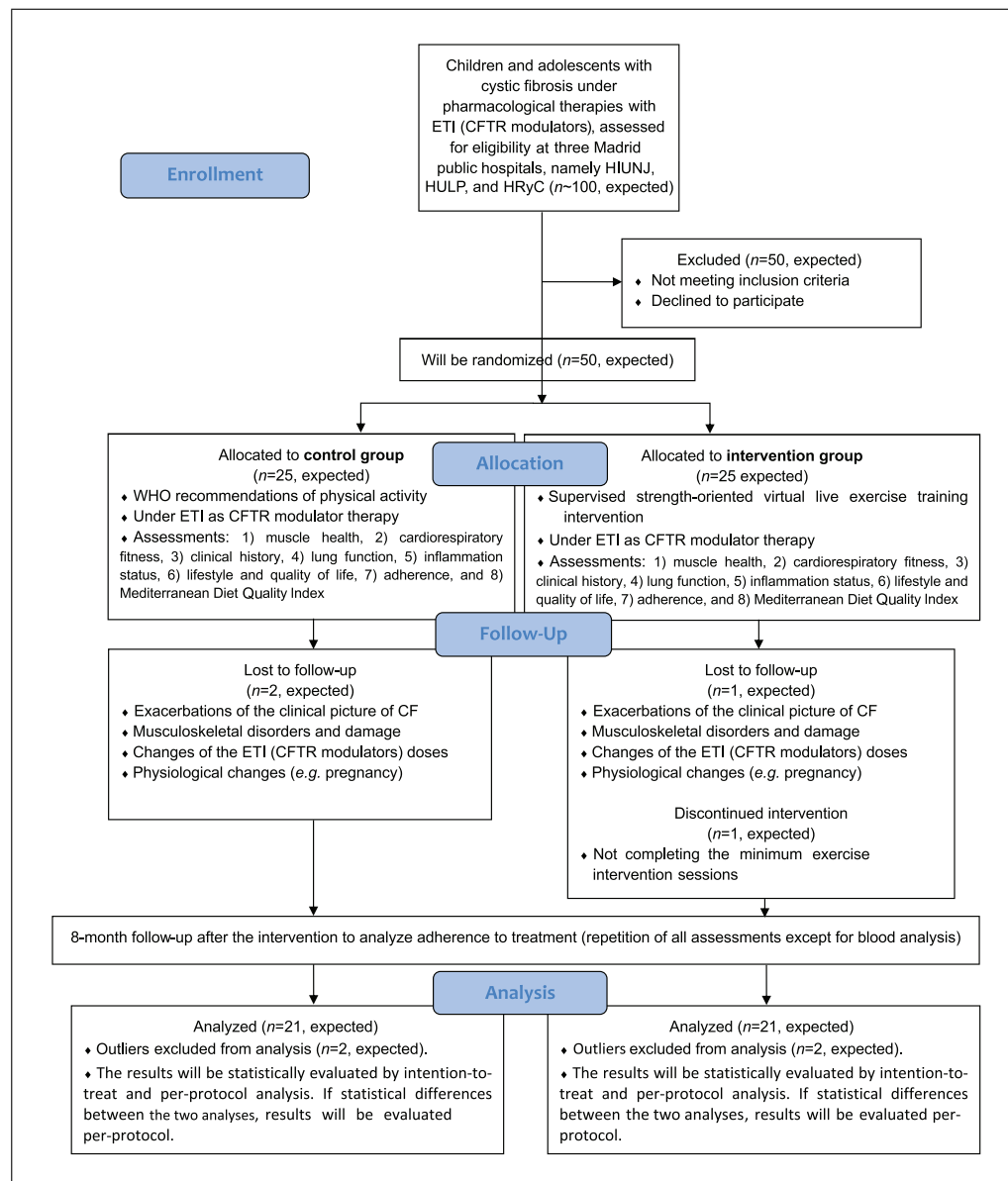


Figure 1 Flow diagram of the FIQMODE randomized controlled trial design following the CONSORT guidelines recommended by the EQUATOR network.

Secondary variables will be pulmonary function, body composition, muscle damage and inflammation-related blood profile, CF lifestyle, and QoL by means of spirometry, bioimpedance, blood analysis, and validated questionnaires. Participants will complete measures at baseline, pre-intervention, and 16 weeks post-intervention.

Ethical Considerations

Trial registration and ethics committee

The FIQMODE Study protocol has been registered on ClinicalTrials.gov (NCT06322446) under the study name “Exercise in People with Cystic Fibrosis on CFTR Modulator Therapy (FIQMODE).” The FIQMODE Study protocol has been approved by the Ethics Committee of the Universidad Politécnica de Madrid (reference number: 20231215, version: 00, date: 08/01/2024) and by the Ethics Committee of the Hospital Infantil Universitario Niño Jesús (HIUNJ; reference number: R-0011/23, version: V3, date: 30/05/2023). An agreement between the Universidad Politécnica de Madrid and the Biomedical Research Foundation (‘Fundación para la Investigación

Biomédica') of HIUNJ (reference number: R-0011/23) was approved on the 30th of May 2023. Subsequent compliance of the Hospital Universitario Ramón y Cajal (HRyC) was approved on the 14th of December 2023 (CEIm 315/23), and compliance of the Hospital Universitario La Paz (HULP) was approved on the 19th of December 2023 (reference number: 2023.895, HULP code: 6618).

Informed consent for participants

Eligible participants with CF and/or their legal representatives (for individuals under the age of 12) will be asked to sign the corresponding informed consent form before study commencement. The principal investigator (PI, M.P.-R.) of the FIQMODE Study, together with the study participant, their parents/legal guardians, and the participant's pediatrician or other primary physician will sign the informed consent form (Supporting Information, APPENDIX 1). The date of informed consent will also be recorded. A signed copy will be shared with each participant, and all original forms will remain in the custody of the PI. The informed consent form of the FIQMODE Study includes a distinct agreement section for supplying an extra blood sample aliquot for research, which can be retracted independently of the other assessments.

Informed consent for image publications

Informed consent forms detailing the publication of images in an open-access manuscript will be accordingly completed by the parents/legal guardians of the children or adolescents whose images will be shown (Supporting Information, Additional File 1).

Study Setting

Demographics and clinical characteristics will be collected at three public hospitals in Madrid, Spain. HIUNJ, HURyC, and HULP will collect information regarding birth date, sex, participant code, height, and weight. HIUNJ, HURyC, and HULP will also collect routine clinical data for individuals with CF regarding chloride measurements and genetic characteristics specifying the presence of the F508del mutation in homozygous and heterozygous children and adolescents, which is the most common mutation in the Caucasian population. Additionally, the hospitals will collect initial routine data regarding pulmonary function [e.g., predicted forced expiratory volume in 1 s (FEV1)], pulmonary microbiology, CF-related pathologies [e.g., CF-related diabetes mellitus (CFRD), pancreatic insufficiency (PI), and CF-associated liver disease (CFLD)], and general CF blood analysis, and additionally, current CF therapies will also be reported [e.g., pancreatic enzyme replacement therapy (PERT), consisting of digestive enzyme capsules containing lipase, protease, and amylase, and insulin or nocturnal enteral nutrition therapies].

Participants

Recruitment

Children and adolescents with CF under pharmacological therapies with CFTR modulators (ETI) will be assessed for eligibility at the three mentioned public hospitals in Madrid ($n \sim 100$ expected). The expected number of children and adolescents will be contacted and invited to participate in the FIQMODE Study. The subjects' pediatrician or other primary physician will contact eligible subjects using a standard telephone call and infographic documents (for the physician and the parents of the children and adolescents) provided by the PI (M.P.-R.) of the FIQMODE Study. The final number of enrolled participants will be selected based on the target sample size, the inclusion-exclusion eligibility criteria, and their agreement (or their parents' or guardians') via the informed consent form. The final number of enrolled participants will be randomized for allocation ($n \sim 50\%$ of the initially enrolled participants expected).

Eligibility criteria

Children and adolescents with CF will be selected according to the following inclusion and exclusion criteria. If any pharmacological initial or prolonged adverse effect is observed, the participant's pediatrician or other primary physician will fill out the adverse effects section of their routinary clinical reports of their assigned hospital. The presence of pharmacological adverse effects will be considered as an exclusion criterion and will be determined by each child's or adolescent's physician according to the Technical Data Sheet for the ETI therapy (CIMA-AEMPS, 2020b).

Enrolled participants who meet the following inclusion criteria will be eligible subjects of study: (1) having clinically stable CF; (2) being 6 to 20 years of age; (3) under ETI therapy with doses in accordance with the guidelines of the Spanish Agency for Medicines and Health Products (AEMPS); (4) able to clearly understand and follow the intervention instructions; (5) available to attend to three follow-up visits and to dedicate at least 45 min to complete online questionnaires related to this study; (6) able to do physical exercise (including the physical capacity to walk, sit, and stand on their own), not restricted by medical advice; (7) able to perform static and dynamic pulmonary function tests; and (8) successfully understanding, reading, and signing the informed consent form or having a parent or guardian who does.

Participants with the following characteristics will be excluded from the study: (1) being simultaneously involved in another research study; (2) having symptoms of pulmonary exacerbation during the past 4 weeks; (3) having other cardiorespiratory lung disease; (4) having musculoskeletal alterations that may affect the intervention assessments; and (5) being pregnant.

Data Collection

Outcomes collection

Data will be collected by the fieldwork investigators (L.P.-A., V.S.-S., A.L.-N., M.R.V., C.M.G., A.M.-T., M.R.A., M.G.-G) directly from the child or adolescent and/or their parents/legal guardians (if applicable, when the participant is under 12 years old). Subjects of study will be treated confidentially, and they will be anonymized. All the data of the participants will be collected through the Research Electronic Data Capture (REDCap) platform, which is a secure web application for building and managing online surveys and databases for academic, clinical, and research purposes. All FIQMODE Study forms will be uploaded and managed from the REDCap platform. The REDCap forms of the FIQMODE Study will be filled out by the pediatricians, by the fieldwork researchers, and by the participant themselves, when applicable. All data will be verified by the statistician (C.Q.-G.) and reviewed by the PI (M.P.-R.), both of whom will not be involved in the data collection phase of the study, thereby ensuring the reliability of the collected data (Supporting Information, Additional File 1).

Retention and study completion

An engaged and cooperative attitude will be anticipated for parents/legal guardians once the informed consent form for the study is signed (Supporting Information, APPENDIX 1). In addition, fieldwork investigators will implement motivational strategies, including interactive methods for children and adolescents: for instance, delivering instructions in a playful way by utilizing amusing stories and humorous names for measurements. Furthermore, motivational seminars will be provided, highlighting the significance of advancements and new research findings related to CF pathology.

Data Management

Confidentiality

The security and confidentiality of participants' personal information will be guaranteed at every phase of the FIQMODE Study RCT. Participants' personal information will be collected at the corresponding hospital where the child or adolescent is first treated by their assigned pediatrician or other primary physician. A routinary clinical history number will be generated at the corresponding hospital as part of the standard hospital protocol. However, an additional participant code for research purposes only will be generated and uploaded to the REDCap application to manage the research data. All codes will be anonymized by using random codes and will not reveal the identity of the subjects.

Data quality

Data will be handled with an anonymous alphanumeric code in "FIQXXXX" format within the REDCap application, which will be utilized for both data collection and secure data management. All participant information, such as consent forms, reports, and logbooks utilized during assessment sessions, will be kept in secure filing cabinets within restricted-access locations. These documents will be recognized solely by the anonymous alphanumeric participant code. All records will follow the same procedure for coding and anonymity.

The names of the participants linked to their corresponding participant codes will be known solely by the PI of the FIQMODE Study (M.P.-R.). Personal data will be stored apart from other information and will be regarded as extremely confidential. It will remain undisclosed to any outside entity, ensuring total confidentiality.

All collected information will be transformed into an electronic format and safely stored in the REDCap database. Furthermore, all forms and questionnaires collected throughout the RCT will be filled out online directly on the REDCap platform. Access to this platform will be exclusively restricted to the researchers of the FIQMODE Study. All the study data will be safeguarded for a minimum of 10 years to ensure the traceability of the data for subsequent tentative scientific publications.

Collection and management plans

Blood sample aliquots will likewise be anonymized by utilizing the secure participant codes. Additionally, they will be registered in the blood collection bank of the Instituto de Salud Carlos III, reference C.0008204, and stored in the -80°C ultra-freezer room of the Biochemistry Laboratory at the Faculty of Physical Activity and Sport Sciences of the Universidad Politécnica de Madrid. The investigator in charge of managing the biological samples will be C.S.-D., who has a doctorate in Biology and Biotechnology.

Randomization and Allocation

Participants will be randomly allocated to the control and exercise groups at a 1:1 ratio, utilizing the stratification approach based on biological sex and age to prevent any imbalance between the groups of the FIQMODE Study intervention. The Python statistical analysis program (version 3.13.3, Python Software Foundation, Beaverton, Oregon, USA) will be employed for allocation purposes.

Allocation concealment will be ensured through a centralized, computer-based randomization with restricted access until confirmation of participant enrollment. This method aligns with CONSORT 2025 recommendations (Hopewell et al., 2025). The concealment allocation strategy that will be applied in the present study ensures adequate treatment assignment and concealment randomization to prevent selection bias in RCTs (Schulz et al., 1995). The FIQMODE Study statistician (C.Q.-G.) will assign the allocations in sealed

envelopes tagged with either “0” or “1” (representing the control or exercise group, respectively) and given to the PI of the FIQMODE Study (M.P.-R.), both blinded to whether “0” or “1” corresponds to the control or exercise group. Unblinding of the outcome assessors is not foreseen in this study. The PI will hand the envelopes to the exercise intervention instructors, T.I. and O.B., each with a PhD in Physical Activity and Sport Sciences. The FIQMODE Study intervention will then be allocated by these instructors of the exercise intervention based on the participant codes provided on the envelopes. Neither the PI (M.P.-R.) and fieldwork investigators nor the pediatricians will know the individual group participant assignment, whether to the control or exercise group, until the end of the study. In summary, the FIQMODE Study statistician (C.Q.-G.) will generate the allocation sequence; pediatricians (V.S.-S., A.L.-N., M.R.V., C.M.G., and A.M.-T.) will enroll participants, and the exercise intervention instructors (T.I. and O.B.) will choose randomly which list they are assigning to either the control or intervention group.

FIQMODE Study Timeline

The timeline and schedule for participants in the FIQMODE Study are shown in Table 1. This table was developed following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.

Strength-Oriented Virtual Live Exercise Training Intervention

Characteristics of the intervention

The supervised strength-oriented virtual live exercise training intervention will follow the recommendations of the Consensus on Exercise Reporting Template (CERT) (Slade, Dionne, Underwood, & Buchbinder, 2016; Slade, Dionne, Underwood, Buchbinder, Beck, et al., 2016). Table 2 contains a summary of the CERT items of the FIQMODE Study. In-depth description of each item is provided in the Supporting Information, APPENDIX 2.

The FIQMODE Study will compare whether the proposed exercise intervention strategies are more effective than the existing usual healthcare protocols for children and adolescents with CF under ETI treatment. The proposed control will serve as a comparator to assess the efficacy and cost-effectiveness of the proposed exercise intervention while ensuring children’s and adolescents’ safety and adhering to ethical standards. This will allow determination of whether the exercise intervention can be adopted in clinical practice for children and adolescents with CF undergoing ETI treatment.

Trial groups

The exercise group will receive a strength-oriented virtual live exercise training intervention for 16 weeks. Exercise training will consist of two sessions of 60 min each per week, with at least 48 hr between sessions. The participants will carry out the exercise from the comfort of their own home with a Physical Activity and Sport Sciences instructor who will oversee and guide their assigned subjects during the 16-week intervention period.

Every session will include 5 min of warming up, 5 min dedicated to core strengthening, 25 to 30 min for strength training, 7 to 10 min of cardiovascular training, and 5 min for cool down. The exercise will be tailored for each subject, customized to their specific needs and following safety precautions specific to the pathogenesis of CF. Heart rate along with the rate of perceived exertion will serve as reference metrics for the Physical Activity and Sport Sciences instructor to assess the training intensity of the participant. It will be advised that all children and adolescents utilize a large space in their home where they can perform the assigned exercises easily and which can be observed through the computer screen.

Table 1 FIQMODE Study Timeline and Participants' SPIRIT Checklist

TIMEPOINT	FIQMODE STUDY TIMELINE						
	Enrollment	Allocation	Post-allocation			Follow-up after the intervention	
	$-T_1$	T_0	T_1	16 weeks	T_2	8 months	T_3
ENROLLMENT:							
Ethics committee application and clinical trial registration	X	–	–	–	–	–	–
Form and questionnaire design in REDCap	X	–	–	–	–	–	–
Recruitment and enrollment	X	–	–	–	–	–	–
Informed consent	X	–	–	–	–	–	–
Eligibility screening	X	–	–	–	–	–	–
Randomization	X	–	–	–	–	–	–
Training protocol and baseline measurements	–	X	–	–	–	–	–
Allocation	–	X	–	–	–	–	–
INTERVENTIONS:							
<i>Exercise group</i>	–	–	X	–	X	–	X
<i>Control group</i>	–	–	X	–	X	–	X
ASSESSMENTS:							
<i>Demographics</i>	–	–	X	–	–	–	–
<i>Clinical history data</i>	–	–	X	–	X	–	X
1) Muscle health	–	–	X	–	X	–	X
2) Cardiorespiratory fitness	–	–	X	–	X	–	X
3) Clinical history	–	–	X	–	X	–	X
4) Lung function	–	–	X	–	X	–	X
5) Inflammation status	–	–	X	–	X	–	X
6) Lifestyle and quality of life	–	–	X	–	X	–	–
7) Adherence	–	–	X	–	X	–	X
8) Mediterranean Diet	–	–	X	–	X	–	X
Quality Index	–	–	X	–	X	–	X

A familiarization session will be carried out prior to the intervention to determine the children's and adolescents' starting physical level and ability to follow an appropriate personalized progression. This familiarization session together with the cardiopulmonary exercise test (CPET) will allow the exercise intervention instructors to plan, progress, and personalize the exercise sessions for each subject of study. Four principal exercises of the intervention will be selected to calculate the estimation of the maximal repetition of 1 exercise, or 1RM [$1RM = \text{lifted weight} \times (1 + 0.0333 \times \text{repetitions})$] from submaximal performance tests, back squats, dead lift, military press, and horizontal rowing, based on the recommendations of LeSuer et al. (1997).

The control group will follow the general recommendations of their physician regarding physical activity, complying with the standard WHO recommendations for physical activity. This group will only be followed up by telephone call sessions to explain the

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Table 2 Summary of the CERT Items of the FIQMODE Study^a

Item category	Item	General description of item
WHAT: materials	1	Set of elastic bands, weights, bars, discs, and kettlebells and a heart rate monitor
WHO: provider	2	Physical Activity and Sport Sciences exercise instructors (researchers)
HOW: delivery	3	Individual exercise training in the presence of an adult for subjects younger than 12 years old
	4	Supervised exercise training
	5	Training Session Adherence Report Form (Supporting Information, APPENDIX 3.2), filled out by the researcher
	6	Engaging workout methods for children and adolescents
	7	Exercise progression will be monitored by the Physical Activity and Sport Sciences researchers using the general monitoring diagram of the progression of the strength exercises (Supporting Information, APPENDIX 2, Figure 1.2). Exercise technique adaptation followed by load progression of $\geq 50\%$ 1RM will be performed.
	8	Illustrations and photography of the exercise training intervention to replicate exercises (Supporting Information, APPENDIX 5)
	9	No specific instructions will be given to the subjects in parallel with the exercise training intervention. However, children and adolescents will followed their routine physical activity curriculum at school.
	10	There will be no other non-exercise components like education, cognitive behavioral therapy, or massage added to the exercise training intervention
	11	Cystic fibrosis adverse effects are listed in the Supporting Information, APPENDIX 3.1 and 3.2, filled out by the researcher. These will be managed using the Zurich medical insurance N° 00000136134616 specifically designed for the FIQMODE Study. Possible adverse effects and their management are described in the Supporting Information, APPENDIX 2, Table 1.
WHERE: location	12	Open, wide space in the home
WHEN, HOW MUCH: dosage	13	Sixteen-week exercise training intervention with two sessions of 60 min per week, with a minimum of 48 hr between the two sessions. The training intensity will be individualized. Each session will consist of familiarization, 5 min of warm-up, 5 min of core strengthening, 25-30 min of strength training, 7-10 min of cardiovascular training, and 5 min of returning to calm (always implemented in this order).
TAILORING: what, how	14	Core, strength, and cardio exercises will be generic types. However, the sessions will be adapted and tailored to the individual.
	15	The decision rule that determines the starting level for exercise will be based on the CRF, lower and upper limb strength, and material adaptation and familiarization
HOW WELL: planned, actual	16	Whether the exercise intervention is delivered and performed as planned will be reported in the “observation” box in the Supporting Information, APPENDIX 3

^a Adapted CERT for the FIQMODE Study. 1RM: maximal repetition of 1 exercise; CRF: cardiorespiratory fitness.

general recommendations for physical activity for their specific age. The Physical Activity Questionnaire for Children (PAQ-C) or Adolescents (PAQ-A) will be administered at the beginning and end of the study to monitor potential physical activity changes. These questionnaires serve as validated self-report instruments for estimating overall physical activity levels in pediatric and adolescent populations. Question 9 in PAC-C and

question 8 in PAC-A will be useful to evaluate whether the children and adolescents are meeting the WHO recommendations. Subjects in the control group will not be trained using virtual strength-oriented personalized exercise sessions. At the end of the FIQMODE Study, if the intervention is proven to be efficient, the control group will be trained for 4 weeks following the same exercise intervention group protocol. In this case, the control group will be provided with material and information to continue with the exercise training sessions.

Participants will be allowed to withdraw from the present study at any time, and their collected data will be analyzed until withdrawal unless requested otherwise. Discontinuing or modifying the allocated intervention is not foreseen unless safety concerns or possible adverse effects that may compromise the integrity of the participants arise (Supporting Information, APPENDIX 2, Table 1).

Motivational strategies will be designed and personalized by the exercise intervention instructors based on each participant's needs to enhance adherence to the intervention protocols. The exercise intervention will not involve economic compensation, and children and adolescents will be given exercise materials free of charge to stimulate and support their motivation. Adherence will be monitored using the Training Session Adherence Report Form (Supporting Information, APPENDIX 3). Heart rate, perceived exertion, types of exercise, and other participant observations will be reported by the exercise intervention instructors using the mentioned adherence form. Additionally, the Visual Analogue Scale of Adherence to Treatment (VASANA) questionnaire will be used to evaluate and improve future adherence strategies (Supporting Information, Additional File 1).

Study Variables

The FIQMODE Study will evaluate the strength-oriented virtual live exercise training intervention using the following study variables: 1) muscle health, 2) CRF, 3) clinical history, 4) lung function, 5) inflammation status, 6) lifestyle and QoL, 7) adherence, and 8) KIDMED.

The clinical relevance of the selected study variables has several justifications, including improvement of QoL and subjects' survival and hospitalization, ease of measurement during routine consultations, and portability and validation.

The exercise training intervention will be carried out using the existing hospital health-care routine clinical protocol, which will also provide post-trial care to the children and adolescents who will be subjects of this study. There are no anticipated risks, and the likelihood of risks that may compromise the safety of subjects during FIQMODE exercise training intervention participation is low. All variables will be measured at baseline (T1), 16 weeks post-intervention (T2), and 8 months after the intervention (T3).

Primary outcomes will be muscle health and CRF, and secondary outcomes will be clinical history, lung function, inflammatory status, lifestyle and QoL, adherence, and KIDMED.

Primary outcomes

(1) Muscle health

Table 3 summarizes the muscle strength assessments.

(1.1) Lower limb muscle strength: polyarticular movement

The maximum isometric strength of the lower limbs will be first measured through polyarticular movement using a portable digital leg dynamometer (Takei 5002 Scientific

Table 3 Summary Description of Muscle Strength Assessments

Muscle strength	Type		Instrument
Lower limb muscle strength	Polyarticular movement	With climbing harness	Digital leg dynamometer, Takei 5002 Scientific Instruments, Niigata, Japan; Climbing harness, Petzl model Corax, Crolles, France
		Without climbing harness	Digital leg dynamometer, Takei 5002 Scientific Instruments, Niigata, Japan
	Monoarticular movement	Flexion	Microfet® II HHD, Hoggan Scientific, Salt Lake City, Utah, USA
		Extension	
Upper limb muscle strength	Hand dynamometry		Jamar Plus+ Hand Dynamometer model 081406453, Fabrication Enterprises, China
	Arm flexion		Microfet® II HHD, Hoggan Scientific, Salt Lake City, Utah, USA
Respiratory muscle strength	Maximal expiratory pressure (MEP)		MicroRPM®, CareFusion, Höchberg, Germany
	Maximal inspiratory pressure (MIP)		

Instruments, Niigata, Japan) following the protocol established by Segovia Martínez et al. (2007). Subjects of study will be positioned on the platform while standing with knees slightly bent at an angle of 120° to 135° and gripping the leg dynamometry bar with both arms extended straight. The fieldwork researcher will adjust the grip chain length according to the height of each participant. In this position, the participant will be asked to exert maximum upward force to carry out a knee extension for 5 s while maintaining a vertical trunk. Two repetitions will be carried out with a 1-min break in between (Supporting Information, Additional File 2, Figure 1). The highest value of the two repetitions will be recorded and then adjusted based on each participant's body weight.

An adaptation of this measurement has also been published by Blain et al. (2006), and this will be implemented in the FIQMODE Study as well. This test modification is carried out using a climbing harness (Petzl model Corax, Crolles, France) to emphasize the movement in the lower limbs while reducing the exerted effort by the upper body and lower limbs. The harness strap will be positioned over the iliac crests of the subject while they maintain a standing standard anthropometric position with knees also slightly bent at an angle of 120° to 135°. The fieldwork researcher will also adjust the grip chain length according to the height of each participant. The rest of the instructions for the execution and for data collection on the maximal leg strength will be the same as the ones described before (Supporting Information, Additional File 2, Figure 2).

(1.2) Lower limb muscle strength: monoarticular movement

The maximum isometric strength of the lower limbs will be measured through monoarticular movements using a Microfet® II hand-held dynamometer (HHD) (Hoggan Scientific, Salt Lake City, Utah, USA) following the protocol of Douma et al. (2014). The isometric strength of the knee flexors and extensors will be assessed while subjects are seated on a massage therapy bed with the knee bent at 90° (the lower leg vertically positioned); the

participant may grasp the edge of the table to ensure stability. The dynamometer will be positioned in the ankle region (in front for the extensors and behind for the flexors).

A stabilized, adjustable, and non-stretchable safety belt will be employed over the Microfet® II HHD to measure the extension following the protocol established by Bohannon et al. (2012) (Supporting Information, Additional File 2, Figure 3). Three alternating repetitions will be performed for each leg, holding tension for 4 to 5 s, followed by a recovery period of 1 min between measurements. Less than 10% variability between repetitions will be ensured, and the same instructions will be applied for testing the isometric strength of the knee flexors (Supporting Information, Additional File 2, Figure 4). The maximum strength exertion values for the three repetitions will be collected and consequently adjusted by each participant's body weight.

(1.3) Upper limb muscle strength: hand dynamometry

Maximum isometric handgrip strength (HGS) will be tested using a digital hand dynamometer (Jamar Plus+ Hand Dynamometer, model 081406453, Fabrication Enterprises, China). Hand dominance will be assessed by inquiring whether the participant's dominant hand is the right, left, or both. The thickness of the dynamometer squeeze will be adjusted based on the size of the participant's hand, typically up to the beginning of the phalanges. The participant will be measured while maintaining a standard anthropometric seated position with a straight back against the backrest, elbows bent to 90°, forearm and wrist in a neutral stance, and both feet flat on the floor (Supporting Information, Additional File 2, Figure 5) (Lopez-Espinoza et al., 2024; Romero-Dapuerto et al., 2019). Each hand will perform two repetitions of maximum isometric HGS for 3 s, alternating hands, with a 1-min rest in between attempts. The maximum value for each hand will be recorded and adjusted to body weight and muscle strength reference values (percentiles) (Ortega et al., 2023). Improvements between 5 and 10 kg will be considered clinically relevant, depending on the baseline values of HGS and exercise adherence (Adair et al., 2021; Bellini et al., 2021; Gibson et al., 2018; Huysentruyt et al., 2019; Sahlberg et al., 2008).

(1.4) Upper limb muscle strength: arm flexion

The maximum isometric strength of elbow flexors will be assessed using the Microfet® II HHD (Hoggan Scientific, Salt Lake City, Utah, USA) (Douma et al., 2014). Subjects will be measured while lying on a massage therapy bed maintaining neutral shoulder position and one elbow bent at 90°, with the other arm resting against the body. The HHD will be positioned on the wrist (near the styloid zone of the wrist). Three repetitions will be performed for each arm alternately, maintaining 4 to 5 s of tension. A recovery time of 1 min between measurements will be employed, with less than 10% variability between repetitions (Supporting Information, Additional File 2, Figure 6). The maximum values of the three repetitions will be considered and adjusted by body weight.

(1.5) Respiratory muscle strength

MEP and MIP will be measured using a respiratory pressure meter (MicroRPM®, CareFusion, Höchberg, Germany) following the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS), which frequently collaborate to publish clinical guidelines and recommendations on various respiratory conditions, including CF (Supporting Information, Additional File 2, Figure 7 (American Thoracic Society, 2002). The participants will take a 5-min break before executing the initial maneuver. Consequently, the participants will execute the maneuvers while seated, maintaining a straight

back and pinching their nose to avoid air leaks. The fieldwork researchers will demonstrate the technique before it is carried out by the participants.

The MEP measurement will consist of inhaling through the nose at the closest maximum inspiratory volume, holding it for 1 s during inspiratory apnea, and subsequently exhaling forcefully through the mouth and into the respiratory pressure meter. Participants will keep their lips tightly sealed around the device while exhaling to avoid air leakage. They will execute the maneuver three times, with a 1-min break between maneuvers. The maximum value from the three repetitions will be recorded.

The MIP measurement will consist of exhaling through the nose at the closest maximum expiratory volume, holding it for 1 s during maximum exhalation, and subsequently inhaling forcefully through the mouth and into the respiratory pressure meter. Participants will accordingly keep their lips tightly sealed around the device while exhaling to avoid air leakage. They will execute the maneuver three times, with a 1-min break between maneuvers. The maximum value from the three repetitions will be recorded.

(1.6) Functional mobility

Participants will perform the 10-m Timed Up and Go (TUG) test. They will begin the test while seated and then quickly walk 10 m, turn around, and quickly walk back and sit back down in the chair (without running). Two repetitions will be performed, and the slowest time will be recorded (Supporting Information, Additional File 2, Figure 8).

(1.7) Sit-to-stand test

The 30-s sit-to-stand test (STS) will be performed using a standard chair with 30 to 40 cm height. Participants will cross their hands over their chest, maintain a straight back, and stand with their feet shoulder-width apart to execute the 30-s STS. Participants will perform as many sit ups (squats) as they can in 30 s. The total number of squats where the participant successfully executes a proper leg extension will be recorded and deemed valid. Two sets of 30 s each of STS will be performed (Supporting Information, Additional File 2, Figure 9) (Jones et al., 1999).

(1.8) Anthropometry and body composition

Anthropometric variables [height (cm), weight (kg), body mass index (BMI, kg/m^2), and waist-to-hip ratio (WHR)] will be collected according to the international standards for anthropometric assessment (The International Society for the Advancement of Kinanthropometry ISAK protocol) (Marfell-Jones et al., 2006).

Body composition will be measured through bioelectrical impedance analysis using the Bodystat 1500MDD Model 17084 (Bodystat, Douglas, Isle of Man, United Kingdom) (Sheikh et al., 2014). Body fat mass (kg, %), lean body mass (kg, %), total body water (%), fat-free mass index (FFMI), and body fat mass index (BFMI) will be recorded (Supporting Information, Additional File 2, Figure 10).

(2) Cardiorespiratory fitness

CRF will be evaluated through an incremental CPET while in an inclined position and at varying speeds on a treadmill (Medisoft RAM model 870A treadmill, Medisoft RAM Italia, Padova, Italia). The protocol will be adapted to the lung size and function of each participant. The protocol will consist of a 2-min warm-up at 3 km/h speed and a 1% treadmill inclination. The speed will increase by 0.5 km/h every 60 s and the inclination

by 1% every 60 s. Gas exchange data will be measured using the Ergostik[®] gas analyzer (Geratherm Respiratory, Bad Kissingen, Germany). Heart rate will be recorded using the Polar[®] H10 heart rate monitor (Polar Electro Oy, Kempele, Finland), and the oxygen saturation (SpO₂) will be measured using the MASIMO SET[®] Rad-97TM pulse oximeter (Masimo Corporation, Irvine, California, USA). The CRF test will be stopped if the oxygen saturation of any child or adolescent falls below 87% at any moment. An adapted Borg scale will be used to assess the perceived central and peripheral effort. Heart rate and oxygen saturation values will be recorded at the beginning of the test, immediately at the end of the test, and at 1 min and 3 min after the end of the test during recovery time.

Ergospirometry will be assessed at rest, at peak, and at ventilatory threshold (VT1), and the following variables will be considered: heart rate, SpO₂, VO₂ (ml/kg/min), VO₂ (l/min), respiratory quotient (RER), ventilation (VE), oxygen (O₂) equivalent (VE/VO₂), carbon dioxide (CO₂) equivalent (VE/VCO₂), respiratory frequency (BF), respiratory reserve (BR), partial pressure of O₂ (PET O₂), partial pressure of CO₂ (PET CO₂), and oxygen pulse and oxygen uptake efficiency slope (OUES). Finally, the VT1, described as the lowest value of the VE/VO₂ without changing the VE/VCO₂, will be measured, and the percentage of VO₂ will be obtained (Supporting Information, Additional File 2, Figure 11).

Secondary outcomes

(3) Clinical history

The clinical history of participants will be recorded to ensure comprehensive data collection throughout the FIQMODE Study. Key parameters will include pancreatic function, diabetes status, and administered pharmacological treatments during the FIQMODE Study period. Microbiological assessments will also be conducted as routine in the hospitals to evaluate potential variations in the participants' microbial composition. Additionally, exacerbations will be documented, quantifying the number, type, and temporal occurrence of each event to identify possible patterns and correlations. Furthermore, sweat chloride levels, measured in milliequivalents per liter (mEq/L), will be analyzed to assess their relevance in the context of the study objectives. This structured approach to clinical history recording will facilitate a thorough evaluation of children's and adolescent's health dynamics and treatment effects.

(4) Lung function

Spirometry will be employed to evaluate respiratory flows and volumes based on key variables, including forced vital capacity (FVC), FEV1, the FEV1/FVC ratio, and forced expiratory flow between 25% and 75% of forced vital capacity (FEF25-75%). A Jaeger[®] Vyntus PNEUMO spirometer (Vyair Medical, Mettawa, Illinois, USA) will be utilized for these assessments, adhering to the technical and critical procedures outlined in the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Graham et al., 2019). The minimum clinically important difference (MCID) for FEV1% in CF has been reported to be 7.1%, serving as a crucial benchmark for evaluating pulmonary function changes (Bhatia et al., 2020) (Supporting Information, Additional File 2, Figure 12).

(5) Inflammation status

Two blood samples will be collected from the cubital vein using Becton-Dickinson Vacutainer[®] vacuum tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA), specifically a 2-ml tube with ethylenediaminetetraacetic acid (EDTA)

Table 4 Muscle Damage and Inflammation Biomarkers^a

Biomarker	Instrument
Muscle damage	
LDH, CK	UV assay based on the rate of NADH formation measured photometrically, which is directly proportional to the catalytic LDH activity, on a Cobas C 311 ^b analyzer (Roche Diagnostics, Basel, Switzerland)
Myoglobin, sTnI	ELISA using DuoSet [®] ELISA Development Systems ELISA Kits ^c (R&D Systems, Bio-Techne, Minneapolis, Minnesota, USA)
Inflammation	
CRP	Immunoturbidimetric assay on a Cobas C 311 ^b analyzer (Roche Diagnostics, Basel, Switzerland)
sTNFR1, serum amyloid A1, calprotectin (S100A8), MPO, MIP-3 α (CCL20), GRO α (CXCL1), I-TAC (CXCL11), Klotho, TGF- β 1, IGF1	ELISA using DuoSet [®] ELISA Development Systems ELISA Kits ^c (R&D Systems, Bio-Techne, Minneapolis, Minnesota, USA)
TNF- α , IL-10, ENA-78 (CXCL5), CCL2/MCP-1, FGF23	ELISA using ELLA Automated Immunoassay System ^d (R&D Systems, Bio-Techne, Minneapolis, Minnesota, USA)

^a CK, creatine kinase; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; LDH, lactate dehydrogenase; MPO, myeloperoxidase; sTnI, serum troponin; TGF- β 1, transforming growth factor β 1; TNF- α , tumor necrosis factor α .

^b Intermediate precision CV: LDH 1.2, CK 0.6, CRP4 1.8. Repeatability CV: LDH 0.7, CK 0.6, CRP4 1.3. CRP4: Tina-quant C-reactive protein IV.

^c Intermediate repeatability CV (ELISA): <10%.

^d Intermediate repeatability CV (ELLA): <7.5%.

3K for plasma collection and a 10-ml tube with dry gel for serum collection. The hospital's nursing service will perform the blood extraction, ensuring that the samples are transported at 4°C within 1 hr to the Biochemistry Laboratory of the Faculty of Physical Activity and Sport Sciences of the Universidad Politécnica de Madrid. Upon arrival, the tubes will undergo centrifugation at 3500 rpm for 15 min, after which 300- μ l aliquots will be prepared in sterile minitubes and stored at -80°C until further analysis.

Serum samples previously stored at -80°C will be analyzed to assess various biomarkers related to muscle damage and inflammation. Muscle damage biomarkers include creatine kinase (CK), myoglobin, lactate dehydrogenase (LDH), and serum troponin (sTnI), which will provide insights into potential muscle injury and metabolic function. Inflammation biomarkers will also be studied, encompassing C-reactive protein (CRP), tumor necrosis factor alpha (TNF- α), soluble TNF receptor 1 (sTNFR1), interleukin 10 (IL-10), serum amyloid A, and calprotectin (S100A8), among others. Additionally, markers such as myeloperoxidase (MPO) and various chemokines—including MIP-3 α (CCL20), ENA-78 (CXCL5), GRO α (CXCL1), I-TAC (CXCL11), and MCP-1 (CCL2)—will be evaluated to investigate immune response mechanisms. Other important biomarkers, such as TGF- β 1, α -Klotho, IGF1, and FGF23, will also be examined to provide further context for inflammatory and metabolic processes. The specific analytical methods applied to each biomarker are detailed in Table 4.

Each DuoSet[®] enzyme-linked immunosorbent assay (ELISA) kit plate (R&D Systems, part of Bio-Techne, Minneapolis, Minnesota, USA) will be used to analyze 40 samples

in duplicate, ensuring precision in measurement. The intra-assay and inter-assay coefficient of variation (CV) will be calculated to assess reproducibility. The manufacturer's instructions will be strictly adhered to throughout the process. For assays conducted using the simplified ELISA (ELLA) Automated Immunoassay System, the operator will be responsible only for dilution and loading of the samples and washing buffer onto the ELLA Automated Immunoassay System (ProteinSimple, part of Bio-Techne, Minneapolis, Minnesota, USA), following the manufacturer's guidelines. Prior to the study, tests will be performed to determine the necessary dilution factor for each case, ensuring optimal assay conditions.

(6) Lifestyle and quality of life

The PAQ-C and PAQ-A will be utilized to evaluate the lifestyle and physical activity (PA) levels of participants aged 8 to 12 years and 13 to 18 years, respectively (Benitez-Porres et al., 2016; Kowalski et al., 1997; Martinez-Gomez et al., 2009). These questionnaires provide a general estimate of physical activity engagement during school hours and after school over the previous 7 days. The PAQ-C consists of 10 questions, whereas the PAQ-A includes 9 questions, with the final question in both versions designed to determine whether the child or adolescent experienced illness or any condition that prevented them from engaging in physical activity. Each question assesses different aspects of physical activity using a five-point Likert scale, and a final score will be derived from the average of 9 questions in the PAQ-C and 8 in the PAQ-A. A score below 2.5 indicates that the participant does not meet the minimum recommended physical activity level. These validated questionnaires serve as effective tools for monitoring physical activity patterns in youth populations.

QoL will be assessed using the validated Cystic Fibrosis Questionnaire-Revised (CFQ-R), a disease-specific instrument designed for individuals with CF (Oliveira et al., 2010). The questionnaire is available in three versions: one for children aged 6 to 13 years, another for parents of children aged 6 to 13 years, and a third for adolescents and adults aged 14 years and older (Quittner et al., 2000). The CFQ-R evaluates 12 key variables related to CF and health-related QoL (HRQoL), including body image, eating disturbance, treatment burden, weight, respiratory symptoms, digestive symptoms, physical functioning, role limitations, vitality, health perception, emotional state, and social state. Each variable is scored on a scale of 0 to 100, with higher scores indicating a better perception of HRQoL.

(7) Adherence

Adherence to treatment will be assessed using a computer application based on the validated VASANA questionnaire (Downey et al., 2015). This tool will evaluate participants' adherence to exercise therapy, ETI treatment, and physiotherapy interventions for CF. The questionnaire is designed to identify potential barriers to adherence and provide a structured approach to monitoring treatment compliance.

(8) Mediterranean Diet Quality Index

Diet quality will be evaluated using the validated KIDMED questionnaire, which measures adherence to the Mediterranean diet in children and adolescents (Serra-Majem et al., 2004). The questionnaire consists of 16 yes/no questions, each assigned a specific score. Based on the total score obtained, dietary quality will be classified into three categories: poor-quality diet (≤ 3 points), need to improve the dietary pattern (4 to 7 points), and optimal Mediterranean diet (≥ 8 points).

Statistical Analysis

Sample size

Assessments of the appropriate sample size have been conducted using Python software (version 3.13.3, Beaverton, Oregon, USA). The effect sizes have been calculated using previous muscle strength variables described by Donadio et al. (2022). A power of 80% for testing two independent samples was considered to identify variations in strength variables between groups, using a significance level of 5% and assuming that the mean for the control group will be 43.30 kg, the mean for the experimental group will be 49.36 kg, and the standard deviation (SD) for both groups will be 17.90 (indicating an improvement of 14% to 15%), a total of 20 participants per group would need to be included. A total of 40 participants with a projected dropout rate of 15% would be required. Therefore, it will be required to enroll at least 50 subjects in total.

Analysis of main variables

Data will be analyzed using Python software, version 3.13 to 3.9, for the statistical computations (Python Software Foundation PSF, Beaverton, Oregon, USA). The significance level for all tests will be set at 0.05. The Shapiro-Wilk test will be conducted to assess whether the data are normally distributed. Differences in baseline characteristics will be determined using parametric tests, *t*-test, or analysis of variance (ANOVA) for data following a normal distribution, and non-parametric alternatives, such as Mann-Whitney's U test or the Kruskal-Wallis test, will be applied for data following a non-normal distribution.

The main analysis will consist of constructing multiple statistical models to examine the effect of the intervention on the outcome variables. For each model, one variable will be designated as the dependent (outcome) variable and the analyzed group (intervention/control) as the independent variable (predictor), in addition to a selection of control covariates. In some cases, a variable that acts as the outcome in one model will be incorporated as a covariate in another to account for its potential confounding effect.

A two-way ANOVA will be conducted to examine the effects of time and intervention on the selected outcome; effect sizes will be quantified using partial eta-squared (η^2_p). If these conditions do not hold—due to missing data, unequal time intervals, or the presence of subject-specific random effects—the analysis will instead use linear mixed-effects models (LMMs) fit with the statsmodels library. LMMs will act as the standard extension of two-way ANOVA when the assumptions are not met and will be estimated by maximum likelihood with random intercepts and slopes as appropriate. The primary interest remains the interaction effects on the outcome, which will be quantified using marginal R^2 (R^2_m) for LMMs, the standard replacement for η^2_p (Nakagawa & Schielzeth, 2013). Specifically, time and intervention variables will be set as fixed effects, allowing subject-specific random intercepts, which can be coded as follows: `mixedlm("outcome ~ time * intervention + cov1 + cov2", data = df, groups = df("subject_id"), re_formula = "~time")`.

Interim analyses

The data will be reviewed periodically to ensure participant safety and trial integrity. The REDCap platform provides the "Data Exports, Reports, and Stats" module, which allows researchers (C.Q.-G., M.R.A., and M.P.-R.) to view reports and inspect plots and descriptive statistics of the data at any point/time of the trial, as well as to export data to CVS files (if access is provided by the PI of the FIQMODE Study, M.P.-R., to the study researchers).

Analysis of concomitant variables

The FIQMODE Study will analyze possible influencing variables (as covariates) of the strength-related variables over the control and exercise intervention groups (as factors) after the study intervention, such as the lifestyle variables and initial CRF [VO₂peak, or >82% of the predicted value according to age and sex (Hebestreit et al., 2019)].

The study does not presently involve any further analyses beyond the planned outcomes. Should any extra or subgroup analysis of variables or confounding factors be required during the study, it will be explained in the final paper and included in a section named “Secondary data analysis.”

Protocol non-adherence and missing data analysis

The FIQMODE Study subjects will be analyzed according to the principle of “per protocol” as well as “intent-to-treat.” In the case of the “intent-to-treat” analysis, missing data will not be imputed to avoid introducing potential bias into the analysis. The use of LMMs allows for robust handling of missing data under the assumption that data are missing at random (MAR). LMMs incorporate all available data points and account for the correlation between repeated measures, reducing the impact of missing data without requiring imputation.

Reasons for dropout and detailed adherence data (attendance logs and VASANA metrics) will be collected and self-reported. The extent and pattern of non-adherence will be summarized by arm to support interpretation of the findings. Sensitivity analyses will be conducted to assess the robustness of the results to differential dropout or non-adherence, using appropriate statistical methods such as multiple imputation or inverse-probability-of-treatment weighting, depending on the characteristics of the missing data (Cohen et al., 2000; Sterne et al., 2009).

Access to the full protocol

Public access to the present protocol document and its subsequent scientific publications will be available in the local projects section of the ImFINE Research Group website (<https://short.upm.es/snkrh>). Access to the full protocol will also be available to all FIQMODE Study researchers using the secure REDCap “File Repository” section (if access is provided by the PI of the FIQMODE Study, M.P.-R., to the study researchers).

Supervision and Monitoring of the FIQMODE Study Protocol

Coordinating parties

The coordinating center of the FIQMODE Study is the Universidad Politécnica de Madrid. The FIQMODE Study management group consists of the PI (M.P.-R.); the coordinators of the FIQMODE Study researcher groups (C.S.-D., M.G.-G., T.Y., L.P.-A., C.Q.-G., M.R.A., A.L.-N., and M.P.-R.); the pediatricians (V.S.-S., A.L.-N., M.R.V., C.M.G., and A.M.-T.); the exercise group instructors (T.I. and O.B.); the fieldwork researchers (L.P.-A., T.Y., and M.P.-R.); the researchers involved in the research design, setup of forms, and scientific writing (L.P.-A., C.Q.-G., and M.P.-R.), and the statistical researchers (C.Q.-G., M.R.A., and M.P.-R.). The trial steering committee of the FIQMODE Study consists of four coordinator researchers (C.Q.-G., M.G.-G., V.S.-S., and M.P.-R.) who will oversee the RCT with scientific rigor. They will monitor the trial’s progress monthly and will ensure the safety of the study subjects. This committee will also provide guidance to the researchers on key aspects of the study and will evaluate and approve significant amendments to the trial protocol, when needed. Any protocol amendments will be reported to both the Ethics Committee of the Universidad Politécnica de Madrid and the ClinicalTrials.gov registration file (NCT06322446, “Exercise in People with Cystic Fibrosis on CFTR Modulator Therapy (FIQMODE)”).

Data monitoring

The data monitoring committee consists of five of the authors the FIQMODE Study: a Doctor of Biology (C.S.-D.), a Doctor of Pharmacy (M.G.-G.), two Doctors of Physical Activity and Sport Sciences (T.Y. and L.P.-A., one a coordinating instructor and the other engaged in physical assessments), a Doctor of Mathematics (C.Q.-G.), a Doctor of Medicine and Surgery (M.R.A.), a Pediatrician (A.L.-N.), and a Sports Medicine Doctor (M.P.-R.). All the mentioned researchers are independent from the sponsor (Instituto de Salud Carlos III), with no competing interests to declare.

Adverse events

If any adverse event is observed during the exercise intervention, adverse event notifications will be directly reported by the parents/guardians to the corresponding subjects' physician. Subsequently, the physician will communicate the reported events to the Physical Activity and Sport Sciences instructors assigned to the corresponding participant. Possible adverse effects and their management are described in the Supporting Information, APPENDIX 2, Table 1.

Study audit

Any modifications to the study will be evaluated and overseen by the coordinators of the FIQMODE Study, who are the same as the data monitoring committee (C.S.-D., M.G.-G., T.Y., L.P.-A., C.Q.-G., M.R.A., A.L.-N., and M.P.-R.). The data monitoring committee will oversee data, questionnaires, forms, computer software, web applications, and data collection documents on a monthly basis. This committee will ensure that the RCT will be accomplished according to the present study protocol.

Dissemination plans

Once the study is completed, all gathered data will be statistically analyzed and published in national and international, peer-reviewed, high-impact, open-access academic journals. Furthermore, the results will be showcased at both national and international conferences related to the fields of Sport Sciences and Sport Medicine. Study results will also be published and reported through degree, master, or doctoral thesis dissertations to be presented at one of the universities involved in this study, Universidad Politécnica de Madrid and/or Universidad Europea de Madrid, and published in their academic repository. All participants' parents/guardians will receive a complete personalized final report of the study results for their own child or adolescent in a pdf-format document.

DISCUSSION

CF is a progressive pathology that may impact muscle health, pulmonary function, and CRF in children and adolescents (Troosters et al., 2009). This condition may also result in recurrent pulmonary infections and severe digestive complications (Ratjen & Doring, 2003). These factors may influence QoL, disease prognosis, hospitalization frequency, and survival rate (Burghard et al., 2022; Perez et al., 2014; Pianosi et al., 2005).

Currently, CF remains an incurable disease, though the introduction of new CFTR modulators has significantly shaped research over the past decade, leading to improvements in QoL and mitigating disease progression. A meta-analysis by Kapouni et al. highlights enhancements in pulmonary function (FEV1%) in both children and adults, alongside weight improvement, reduced pulmonary exacerbations, and improved QoL (Kapouni et al., 2023). The highly effective modulator combination ETI was approved in Spain for people with CF aged >12 years in 2020, with its usage expanded to individuals aged >6 years in September 2022 (Dwight & Marshall, 2021).

Alongside pharmacological treatments, exercise, respiratory physiotherapy, and nutrition have been key components in managing CF, contributing to QoL improvements. Systematic reviews of exercise-based interventions report positive outcomes and emphasize the need for reproducible exercise protocols, which are currently lacking in CF (Garcia-Perez-de-Sevilla et al., 2022; Radtke et al., 2022). This study aims to determine whether personalized exercise, combined with new pharmacological treatments, enhances muscle health, cardiovascular fitness, pulmonary function, and body composition. Additionally, it proposes the integration of individualized exercise regimens for each child or adolescent with CF.

Various exercise interventions exist, but adherence to the CERT ensures a standardized methodology, covering details such as materials, providers, delivery, location, and dosage (Hay-Smith et al., 2019). Replication of RCTs and clinical applications remain limited due to insufficient descriptions of exercise interventions. Seeking better reproducibility and standardization, international organizations advocating for high-quality methodological frameworks, such as the EQUATOR network, recommend using the CERT consensus (Slade, Dionne, Underwood, & Buchbinder, 2016; Slade, Dionne, Underwood, Buchbinder, Beck, et al., 2016).

Applying the CERT improves the quality and transparency of reporting standards in scientific research, enabling the use of data extraction tools to assess intervention homogeneity. Previous studies have employed the CERT in pelvic floor rehabilitation (Fukuda et al., 2023), type 2 diabetes (Hacke et al., 2022), osteoporosis (Mack et al., 2018), and cognitive health in aging (AGUEDA study) (Fernandez-Gamez et al., 2023). However, no RCT-based exercise interventions following CERT guidelines have been reported for CF. Although some studies since 2016 have adopted the CERT, none has focused on CF. Therefore, the FIQMODE Study presents a structured exercise protocol for children and adolescents with CF receiving CFTR modulator therapy.

Strengths and Limitations

The most distinctive strength of the FIQMODE Study is its alignment with the CERT consensus and its subsequent implementation within this research, integrating it into the medical and clinical context as part of CF treatment. The CERT consensus ensures the study's replicability, as it provides a standardized framework for describing all key aspects of the program, including intensity, duration, and supervision. This comprehensive documentation will allow other clinical professionals to accurately replicate the study, ensuring consistency in future research and implementation. The FIQMODE Study will provide hospitals with simple and easy-to-perform assessments of muscular functional capacity, lifestyle, physical condition, and CRF for the pediatric population with CF; additionally, it will provide a strength-oriented virtual exercise intervention that follows the CERT consensus.

Despite the strengths of the FIQMODE Study, several limitations should be acknowledged. The generalizability of the findings may be constrained by the specific characteristics of the sample and the context in which the intervention will be implemented. Furthermore, technology-based home interventions may encounter challenges such as unequal access to digital devices or internet connectivity, as well as variability in the family setting. Lastly, the FIQMODE Study long-term follow-ups could be compromised by the risk of participant attrition, potentially affecting the sustainability of the observed outcomes. Given that the study will be conducted in the context of a rare disease, the number of assessed participants will be limited. Another limitation of this study is the potential presence of aggravations due to medical care requirements associated with symptom exacerbation related to CF. Additionally, a lack of motivation stemming from the nature of the disease could be observed in children and adolescents. Finally, the involvement of

their parents during the study might result in scheduling challenges for the researchers in conducting the intervention.

CONCLUSIONS

The FIQMODE Study protocol is a replicable and safe strength-oriented virtual live exercise training intervention with clinical and research applications for the pediatric and adolescent populations with CF under ETI as CFTR modulator therapy. The FIQMODE Study represents an innovative strategy for managing CF due to its ease of application and reproducibility. Until now, exercise intervention in research as well as in clinical practice did not include or allow the assessment of specific and personalized exercise and did not specify the type or dosage of the recommended exercise. The FIQMODE Study protocol is one of the first pioneering studies with reliable methodology, consistent validity and quality, and, above all, the potential for reproducibility.

TRIAL STATUS

The FIQMODE Study protocol has been approved by the Ethics Committee of the Universidad Politécnica de Madrid (reference number: 20231215, version: 00, date: 08/01/2024) and by the Ethics Committee of HIUNJ (reference number: R-0011/23, version: V3, date: 30/05/2023). An agreement between the Universidad Politécnica de Madrid and the Biomedical Research Foundation ('Fundación para la Investigación Biomédica') of HIUNJ (reference number: R-0011/23) was approved on the 30th of May 2023. Subsequent compliance of HRyC was approved on the 14th of December 2023 (CEIm 315/23), and compliance of HULP was approved on the 19th of December 2023 (reference number: 2023.895 and HULP code: 6618). The FIQMODE Study protocol has been registered on ClinicalTrials.gov under the study name "Exercise in People with Cystic Fibrosis on CFTR Modulator Therapy (FIQMODE)" (NCT06322446).

The first contact with children and adolescents with CF at the mentioned hospitals was on February 27, 2024, and the anticipated completion date for the recruitment is March 23, 2026.

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AUTHOR CONTRIBUTIONS

Lisset Pantoja-Arévalo: Investigation; resources; software; visualization; writing - original draft; writing - review and editing. **Thomas Yvert:** Investigation; methodology; resources; validation; visualization. **Tamara Iturriaga:** Investigation; validation. **Verónica Sanz-Santiago:** Conceptualization; investigation; resources. **Olga Barceló:** Investigation; resources; visualization. **Carlos Quesada-González:** Conceptualization; data curation; formal analysis; investigation; methodology; writing - review and editing. **Ana Morales-Tirado:** Investigation; resources; supervision. **Catalina Santiago-Dorrego:** Conceptualization; investigation; validation. **Alejandro López-Neyra:** Investigation; methodology; supervision. **Marta Ruiz de Valbuena:** Investigation; supervision; visualization. **Cristina de Manuel Gómez:** Investigation; resources; writing

- review and editing. **Margarita Rubio Alonso:** Data curation; formal analysis; investigation; methodology; supervision; writing - review and editing. **Silvia de Vidania:** Investigation; methodology; validation. **Carmen Ramírez-Castillejo:** Investigation; supervision. **Marcela González-Gross:** Investigation; supervision; visualization. **Margarita Pérez-Ruiz:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing - original draft; writing - review and editing.

CONFLICT OF INTEREST

The authors declare that the medical doctors affiliated with HIUNJ have received conference grants financed by Vertex Pharmaceuticals Incorporated, which were utilized in this study. However, no specific payment or financial support has been received from Vertex Pharmaceuticals Incorporated for the conduct of the FIQMODE Study, ensuring that the research remains independent and unbiased.

The rest of the authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Public access to the present protocol document and its subsequent scientific publications will be available in the local projects section of the ImFINE Research Group website (<https://short.upm.es/snrh>). Access to the full protocol will also be available to all FIQMODE Study researchers using the secure REDCap “File Repository” section (if access is provided by the PI of the FIQMODE Study, M.P.-R., to the study researchers).

Supporting Information

cpz170202-sup-0001-SuppMat.pdf

Appendix 1 to Appendix 5: Informed consent forms, FIQMODE-CERT description, adherence report form, exercise training intervention characteristics, exercise training intervention pictures, and FIQMODE SPIRIT checklist.

cpz170202-sup-0002-SuppMat.pdf

Additional File 1: Informed consent model for capturing and using the patient’s image and VASANA questionnaire.

cpz170202-sup-0003-SuppMat.pdf

Additional File 2: Images and illustrations of the measurements of the FIQMODE Study variables.

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