# NETWORK STUDY OF SUPPLEMENTATION OF LINOLEIC ACID IN CYSTIC FIBROSIS

# (NETLACF)

## A DOUBLE-BLIND CONTROLLED RANDOMIZED STUDY OF SUPPLEMENTATION OF LINOLEIC ACID DURING ONE YEAR TO PATIENTS WITH CYSTIC FIBROSIS – Influence on clinical status and metabolism

**Study Protocol**

**August 2020**

# Protocol for NETLACF study

**Aim:** To compare growth, lung function, inflammatory markers and metabolism in a double-blind study of patients given linoleic acid supplementation or oleic acid supplementation combined with omega-3 fatty acids during one year.

**Ethical approval:** The approvals indicate that informed consent from patients and parents shall be obtained.

**Inclusion criteria:** Patients with two "severe" mutation of CFTR, mainly dF508, and pancreatic insufficiency, aged 5-15 years. Since the patients are included from different centres which might have a little different basic treatment, it is desirable that two patients are selected for randomization, who are rather similar in age and disease activity. The patients should not have had extra fatty acids supplementation for the latest 2 months before inclusion in the study.

**Exclusion criteria**: Patient less than 5 years, and older than 15 years. Pregnancy. Transplantation or waiting list for tx. Severe liver disease and/or portal hypertension. Other non-CF related diseases.

**Patients:** Ninty-patients will be included (40 in Poznan, 40 in Milan and 10 in Oslo). The patients will preferably be included at time of yearly check-up, which will decline the burden of investigations at start and end of treatment. All patients shall continue their ordinary treatment and ordinary diet, but may need some extra PERT. They will have their ordinary visits at the CF clinic and be treated as usual at pulmonary exacerbations, which all will be notified in the protocol. The patient will be on supplements for one year.

**Design:** The patients are randomized to either

- group A, who will receive 13 g of linoleic acid (LA) g with 800 mg DHA
- group B, who will receive 13 g of oleic acid (OA) with 800 mg DHA

This design will give the same amount of calories to both groups, Neither staff or patients know to which group they belong. Randomization is made by one not included in the study.

**Methods:**

1. **Anthropometry.**

Height and weight are controlled regularly at the patients´ regular visits to the CF centre but at least at start, 6 months and end of study at 12 months. BMI is calculated and z-scores (SDS) of height, weight and BMI (related to WHO standards). DXA (double X-ray

absorptiometry) is performed at start and end of study for determination of lean body mass, fat mass and bone mineral density.

2. **Food registration.**
   In order to have a check that the participants will not change their ordinary good habits during the study period, a food frequency questionnaire (FFQ) will be used. This will be made at start, 6 months and end of study. The purpose is mainly to register the fat intake and a 24-hr recall shall be added to get an idea of trade marks (the content of type and amount of fat will be different in different countries), size and number of meals to better evaluate the FFQ.

3. **Pulmonary function**
   Routine pulmonary function tests at start and end of study. $FEV_1$ (forced expiratory volume during 1 sec) at each visit.
   - Exhaled NO at start and end of study.
   - Ergometer test at start and end with oxygen saturation (if available)
   - Diffusion capacity
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4. **Biochemistry.**
   Routine blood biochemistry (fasting) at start and end of treatment period, including HB, plateles, white blood cell count and differential count. Liver tests including ASA, ALAT, alkaline phosphatase, GGT, PK, bilirubin (total and conjugated). Cholesterol, HDL, LDL, triglycerides. Urea, glomerular filtration rate. IgG, CRP, sedimentation rate.
   - 1 ml plasma divided in 4 tubes for later analyses to be stored in freezer ($-80^{o}$) for analyses of bile acids, IGF-I, lipid mediators.
   - 0.5 ml plasma for analyses of phospholipid fatty acids to be stored in freezer ($-80^{o}$)
   - 0.5 ml for cytokines

   Urine samples for routine tests

5. **Intestinal function tests**. (Maybe only performed in Poznan).
   - Fecal calprotectin at start and 12 months.
   - Fat absorption at start and 12 months., preferably with 3 days dietary recording to calculate fat absorption coefficient.

6. **Metabolic tests.**
   Indirect calorimetry at start and 12 months.
   Sweat test at start and 12 months, with determination of both SODIUM and chloride
   Urine sample,
   - for 8-isoprostane and eicosanoid metabolites to be stored in freezer($-80^{o}$)

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7. **Compliance and CF Questoinnare for QoL**
8. **Statistics**
   All protocols gathered for analyses at one center.

**Primary outcome**

**Growth BMI (SDS)**

**Secondary outcome**

**Pulmonary function, FEV1.**

**Exploratory outcomes**

**Reduction in exacerbations**

**Normalization of fatty acids profile in intervention group**

**Improvement in liver function tests**

**Improvement lipid mediators**

**Improvement in cytokines**

**Improvement in energy expenditure.**

**Improvement in intestinal function.**

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