“Osteopathic Treatment of Liver and Biliary Tracts in Cystic Fibrosis”

On Planning and Submission of an Osteopathic Clinical Study
to an Ethics Commission
Study Protocol and Application

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Abstract

This master these is an example of the submission an osteopathic clinical study to an ethics commission.
It shows the planning procedure backgrounds and results of the controlled, randomized pilot study on osteopathic treatment of the liver and biliary tracts in cystic fibroses (CF). The study will be conducted in total compliance with the Helsinki declaration.

Careful and professional planning is obligatory for a good clinical study.
This has to consider both scientific and formal-administrative aspects.
To be able to fulfill these criteria, it is absolutely necessary to cooperate with clinically experienced scientists (physicians, biometricians).

This paper includes the planning phase, the protocol, the case report form, the application form and the informed consent form of the pilot study on osteopathic treatment of the hepatobiliary system in CF.

The drafting of the study protocol is like going through a checklist for avoidance of sources of error, to assess in advance security of the patients, statistical evaluation possibilities and organizational and legal aspects.

This paper could be a model for osteopaths and osteopathic students who are interested in the management and planning procedure of osteopathic clinical studies.

Foreword

This paper is an example of the submission an osteopathic clinical study to an ethics commission. As I found out how difficult it is to get the right advice to draft a legally and scientifically correct concept, it is my intention to pass on the information as unfiltered and unchanged as possible. For this reason I have also decided to leave the individual sections as in the original.

Acknowledgments

I would like to thank all those who stood by me with advice and patience. Particular thanks go to Dr. Wolfgang Schimetta for his professional guidance, my partner Gunther for the many hours of discussion and my children Manu, Samuel and Noah for their patience.
Great thanks also go of course to Primarius Dr. Andreas Kainz, who made submission of the clinical study to the ethics commission possible.

Thank you

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1. Planning Phase of the Clinical Study – Guidelines, Background and Results

1.1. Planning

Planning of the study began with literary research and many conversations with patients, colleagues, doctors and tutors of the Master's thesis. First, I wanted to perform only a small investigation until I determined that the topic was so interesting that I gained physicians for collaboration provided that there is a consent of the ethics commission.

After more precise research it turned out that presentation of the study to the ethics commission was not only necessary simply due to the randomization but also favorable for upgrading the evaluation of the study. The approval of an ethics commission for a clinical study doesn't seem so important at first glance. I had to rethink my opinion during the drafting of the study record under the advice of Dr. Wolfgang Schimetta, which was indeed fascinating. This instance is absolutely necessary particularly in terms of quality assurance of Studies. My paper achieved new dimensions through the precise planning of the course of the study, data acquisition and statistical planning.
On one hand there is of course the personal security of the patients, their data protection, and also the legal protection of the performer of the study in terms of possible legal actions. On the other hand sources of error can also be identified in advance and minimized.

The prerequisites for clinical studies are anchored in several bills of law (Helsinki Declaration) which represent quality assurance of the clinical studies. Besides the regulations of data protection, the guidelines of "Good Clinical Practice" (GCP) should be observed in the planning of a study (Weiß 2002).
Good planning regulates the quality of a clinical study.

Legal issues on submission of this study could only be answered with difficulty, as within the area of responsibility of the ethics commissions in Austria legal regulations only exist for medicines and for clinical studies; analogous applications of this law lie within the judgment of the individual ethics commissions. The established area resp. studies not subject to the law relating to the manufacture and distribution of medicines are then borderline areas and decisions are made by the individual ethics commissions, which are not inter-accountable.

Analogous application of "seeding trials" is excluded by randomization.

1.2. Ethics Commission Submission Procedure

For an official submission it is necessary to provide all required documents complete and in the required copies according to each ethics commission.

Together with the application for the ethics commission the study record (including abstract, procedural schema, address list and signatures of the collaborators), the CRF and the ICFs as well as the qualification certificates of the applicant are to be enclosed. For studies with minors the respective ICFs are to be enclosed for both each age group and the parents/guardians.

On the application itself is to be said that it is favorable when this is submitted by a doctor, as it practically never happens (apart from an ethics commissions bound to a University), that these are submitted by a non-physician, although theoretically such are entitled to as long as they handle in their area of responsibility .
For un-sponsored studies there is the possibility of making an application for remission of the processing costs contribution with the ethics commission.

The responsibility of the ethics commissions depends on the location of the validation centre. The validation centre for the objective study is in Schleißheim, Upper Austria, and so the Ethics Commission Upper Austria is responsible.

1.3. Difficulties

Standardization of Osteopathic Treatment:

There is disunity on possible standardization of osteopathic treatment amongst the "experts." The common opinion of colleagues: "The nature of osteopathy is individual treatment of patients, and individual treatment cannot be standardized," is not very satisfactory for the drafting of a study record.

How can one then standardize an individual treatment in order to satisfy physicians and statisticians? Can the efficacy of a holistic method be represented at all with medical parameters?

The suggestion to avoid prospective standardization providing a so called "black box" with retrospective listing of treatment modalities in the annex of the paper was rejected by the statistician with the following words*: "don't upset the statisticians!"* (Sommerfeld 2004/ Schimetta 2006)

As there are international efforts toward standardization of osteopathic training and careers by all European osteopathic organizations (EFO, FORE and OSEAN) and worldwide of the WOHO (World Osteopathic Health Organization) and OIA (Osteopathic International Alliance) (Engel 2006) there must also be standards in the osteopathic treatment of the hepatobiliary system.
Therefore and on the basis of other scientific papers (Marcer 2003, Mills et al 2003) I decided to define a package of treatment: General osteopathic techniques of the hepatobiliary system and other osteopathic techniques when necessary, to leave open individual treatment and so not violate osteopathic principles.

Lacking Clinical Experience

Although the fostering of research activities on efficacy and mechanisms in osteopathy pursuant to the Lannoye Report are discussed as an Austrian career policy goals (Engel 2006), the lack of clinical research in this area is particularly attributed to lack of financial support and ancillary training (Sommerfeld et al. 2004).

Legal Clarification

The ethics commission lawyers were naturally interested in the legal basis on which a physiotherapist has the authorization for the performance of a visceral treatment.

Availability of Competent Persons

In the current situation, it is difficult to find competent persons in osteopathic scientific issues. Firstly there are only a few of them and secondly they are only assigned with the support of students as an ancillary role or only come to Austria for guest lectures.

To be able to perform scientifically and legally correct planning of a clinical study and drafting of a study record, it is necessary to cooperate with experienced scientists.

1.4. On the Ethics Commission Upper Austria

The Ethics Commission Upper Austria is situated in Landesnervenklinik Upper Austria Wagner Jauregg, Linz, under the direction of Prof. Dr. Johannes Fischer.
First contact and enquiries to the ethics commission were rather unfavorable, partially also due to lack of bilateral knowledge with the handling of this precedence case.
On my part it would have been necessary to already submit a working version of the study record to the ethics commission for any arising questions.

1.5. Presentation and Feedback

The official submission of the osteopathic clinical study was on 17 October 2006, and the meeting of the ethics commission was set for 8 November 15:50.

The study was handled briefly and concisely in a congenial atmosphere. After a short presentation of the study, the study record was discussed, a report on possible risks read out by an expert (I have unfortunately no access to this report), and various questions of the commission were answered.

The study record was very positively assessed; only the statistical section still had to be reworked.
The risk for the patients was assessed as low and further funding for additional insurance were therefore waived.
An extension of the patient information for childbearing women was to be submitted later.
The processing costs contribution was waived by the ethics commission.

1.6. The decision of the Ethics Commission

The ethics commission issued a positive decision for the performance of the clinical study for 12 months on 23.11.06 (see annex). For an extension of the study duration, an application and a study report (ethics commission form) had to be submitted.

1.7. Schedule

The chronological course of the submission of the concept to the Donau -University Krems up to beginning of the study in overview:

January 2006	Submission of the study concept to the Donau – University Krems Acceptance
February-May 2006	Research; contacts with Cystic Fibroses - centers; reworking of the concept, needs assessment and patient recruitment
May 2006	First contacts with various ethics commissions and definition of responsibility.
20 May 2006	First written enquiry for an official submission of the clinical study to the Ethics Commission in Upper Austria
18 June 2006	Confirmation of application to the Ethics Commission in Upper Austria by a doctor authorized to perform studies.
June – October 2006	Drafting of the study record with Dr. W. Schimetta definition of the legal status
17 October 2006	Submission of the application for the clinical study
8 November 2006	Meeting of the Ethics Commission Upper Austria
14 November 2006	Written demand for corrections
20 November 2006	Submission of corrections
23 November 2006	Positive decision of the Ethics Commission Upper Austria limited to 12 months.
	Final administrative preparations, patient recruitment The planning phase will end with the "first patient in."

1.8. Discussion

Careful and professional planning is obligatory for a good clinical study.
This has to consider both scientific and formal-administrative aspects.
To be able to fulfill these criteria, it is absolutely necessary to cooperate with clinically experienced scientists (physicians, biometricians).
For enquiries and procedures with the ethics commission one should already be able to present careful planning (study protocol).

Dealing with the planning of this clinical study and the ethics commission, but particularly the cooperation with Dr. W. Schimetta has allowed me a different insight into scientific papers. For me the drafting of the study protocol was like going through a checklist for avoidance of sources of error, to assess in advance security of the patients, statistical evaluation possibilities and organizational and legal aspects.

A future vision, also from career policy view for Austrian further development of osteopathy is the planning of a research department bound to the university or the formation of scientific circles, not only to make financing of studies possible but rather also to enable expertise in the development and performance of clinical studies and also of new osteopathic methods.

Through my paper I hope to serve as a example for subsequent students or osteopaths who decide on a clinical study, showing them how a study protocol can look and showing them many paths, and maybe also a few shortcuts.
In the annex are addresses and websites at which information can be found to find resp. requested.

1.9. Bibliography

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Discussions:

Dr. Wolfgang Schimetta, Biometric, July-Oct 2006

1. The Study Protocol

2.1. Basic remarks

The study protocol is the core of every study and is the prerequisite for all further steps. This is about developing an idea into a "clear concept."

The drafting of the objective study protocol was achieved through advice from Dr. Wolfgang Schimetta, who also performed the biometric testing planning.

The structure of the study protocol was precisely specified chapter by chapter.
At the beginning is an address list with the collaborators of the study followed by a brief summary and procedure plan. It is important in this part to prepare as much information as possible simply and clearly, as the majority of the ethics commission only receive this section of the study protocol.

In the main section the purpose of the study, the background, target parameters, biometric testing planning and legal, ethical, and administrative aspects are handled.
Most voluminous are the legally and scientifically correct formulations on the individual topics.
It is recommendable to perform the drafting of the study protocol with a clinically experienced colleague or biometrician.

2.2. The Study Protocol – Final Version

"Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses"

A controlled, randomized pilot study on osteopathic treatment of the hepatobiliary system in cystic fibrosis

Version: 4 October 2006

Correction: November 2006

2.2.1. Names and addresses

Medical Director of Studies	**Prim. Dr. Andreas Kainz**
Non-medical Director of Studies	**Olivia Maier** Graduate Physiotherapist and Osteopath
Test center:	**Practice for Osteopathy** Pfeffergasse 20/1 4600 Schleißheim Mobile: 0650/2076560 E-mail: olivia.maier@telering.at
Statistician:	**Mag. Johannes Reichl** **Dr. Wolgang Schimetta**
Referring doctors:	**See list, separate document**

2.2.2. Summary

Title:

"Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses"

Background and objectives:

Cystic fibrosis (CF) is the most common genetically-inherited, autosomal recessive disease of the Caucasian population. The typical CG mucous obstructs the gallbladder and pancreas and prevents the digestive enzymes and bile from reaching the duodenum and the small intestine in order to help break down and digest the food. The consequences of the bile backlog secondarily result in inflammations of the liver parenchyma, and thus in typical fibrotic transformation of the liver and liver cirrhosis. Liver disease is the cause of 5% of the deaths of CF patients (Eisenburg 1992; Lang 2001; Götz 2004).
CF patients often suffer from abdominal pain (Claaß et al 2004), wind, foul-smelling stools and maldigestion.

This pilot study shall serve to identify the influence of a 12-month osteopathic treatment series on the liver and biliary tracts in CF.

Working hypothesis:

Osteopathic treatment of the hepatobiliary system in CF leads to an improvement in the transport of bile acid. It reduces inflammation processes in the liver parenchyma and reduces abdominal pain and wind and therefore improves the quality of life for these patients.

Design of the study:

Open, monocentric, controlled, randomized pilot study in parallel group design.

Study participants:

In total, 36 patients will be included (Intention-To-Treat by lot).
18 patients per group (20% drop-out quote - approx. 15 valid cases for efficacy per group in per protocol collective).

2 intervention groups:

O group: Osteopathic group – in addition to medical and physiotherapeutic standard therapies, they receive osteopathic treatment.

K group: Control group – receive medical and physiotherapeutic standard therapies.

Inclusion criteria:

- Cystic fibrosis
- Age 8 -99 years old
- Pancreas insufficiency
- Personal consent (& consent of a legal guardian)
- Last annual examination by the treating doctor may not be older than 3 months
- Availability

Exclusion criteria:

- Liver cirrhosis
- Aortic aneurysm
- Liver, gall, stomach and pancreas tumors
- Known pregnancy
- Desire to have children in the treatment period in childbearing women

Study intervention: Only O group

Total:

9 x Osteopathic treatments of the hepatobiliary system à 30 min,

Treatment intervals of 6 weeks (+/- 2 weeks)

Active phase per patient is in total 12 months (+/- 3 weeks).

Accompanying intervention:

Medical and physiotherapeutic standard therapies.

Recruiting patients:

The recruiting phase will last 24 months. If not all 36 patients are included within this period, the study will be concluded with the attained number of cases.

Study procedure:

- Establishing contact through the referring doctor
- Determination of the inclusion and exclusion criteria
- Obtaining the consent of the patients
- Initial examination E1
- Randomization
- Intervention phase 1
- Intermediate examination IE (3 months after E1 +/-2 weeks)
- Intervention phase 2
- Final examination E2 (12 months after E1 +/-3 weeks)

Target parameters and groups:

2. Change from E1 to E2:

   CFQ-R, visual analog pain scale, bile acid, liver function, ultrasound, clotting factors, medication

3. Changes from 12 months before the start of the study to the study participation

   Hospital stays

4. Change from E1 to IE:

   CFQ-R, visual analog pain scale and medication

5. Change from IE to E2:

   CFQ-R, visual analog pain scale and medication

Data recording / data protection

The patient data will be protected by issuing identification numbers.

Statistics:

- 2 groups
- Stratification according to provinces
- Analysis:
  - Target parameter – per protocol
  - Safety parameter – Intention-to-treat
- Formation of subgroups
  - Assigning province
  - CFQ-R under 14 years old versus CFQ-R over 14 years old
- Descriptive and statistic analysis

Duration of study :

36 months

Ethical aspect:

The potential benefits in the O group are confronted with a practically non-existing and/or irrelevant risk.

In the K group there is no deviation from the routine.

Insurance:

The osteopathic treatment is non-invasive and is not linked to any relevant risk.

All medical examinations are in accordance with the routine checks.

Test center:

Practice for Osteopathy

Pfeffergasse 20/1

4600 Schleißheim

Mobile: + 43 650/2076560 E-mail: olivia.maier@telering.at

Publication:

A publication of the study results is obligatory.

Initial author:

Olivia Maier, Osteopath, Graduate Physiotherapist

Co-authors:

Prim. Dr. Andreas Kainz, D.O. Osteopath, Medical Specialist for Physical Medicine

Mag. Johannes Reichl, Statistician

Authoritative referring doctors

2.2.3. Procedure Plan

“Osteopathic Treatments of the Hepatobiliary System in Mucoviscidosis”

Figure 2: Course of the study for a patient

				Active Phase - 12 months (+/- 3 weeks)			
		Start		Intervention phase 1 approx. 3 months		Intervention phase 2 approx. 9 months	
O group	C	E1	R	Osteop. treatment standard therapy	IE	Osteop. treatment standard therapy	E2
K group	C	E1	R	Standard therapy	IE	Standard therapy	E2

R = Randomization

C = Establishing contact

E1 = Examination 1

E2 = Examination 2

IE = Intermediate examination

Total duration of study: 36 months

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2.2.22.3. Subgroup analyses

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2.2.24. Ethical aspects

2.2.25. Insurance

2.2.26. Publishing results

2.2.27. Responsibilities

2.2.28. Appendix protocol:

- **Detailed description of methods**
- **Index of abbreviations**
- **Bibliography**
- **Sealed randomization list (copy)**
- **Visual analogue pain scale**
- **CFQ-R (see appendix master these)**

2.2.5. Introduction

Cystic fibrosis (CF) is the most common genetically-inherited, autosomal recessive disease of the Caucasian population. In North America and Europe the incidence lies between 1/2500 and 1/1600 (Gallati 2001). Due to the faulty transport of sodium and chloride within the cells that line organs such as the lungs, liver, gallbladder, pancreas and the skin, the body produces abnormally thick, sticky mucous. The typical CG mucous obstructs the gallbladder and pancreas and prevents the digestive enzymes and bile from reaching the duodenum and the small intestine in order to help break down and digest the food. The consequences of the bile backlog secondarily result in inflammations of the liver parenchyma, and thus in typical fibrotic transformation of the liver and liver cirrhosis.
Liver disease is the cause of 5% of the deaths of CF patients (Eisenburg 1992; Lang 2001; Götz 2004).

CF patients often suffer from abdominal pain (Claaß et al 2004), wind, foul-smelling, fatty stools and maldigestion. Special diets and the substitution of the pancreas enzyme and ursodeoxycholic acid have significantly improved this ailment. However, almost all CF patients are at least latently affected by a reduced function of the hepatobiliary system and - with increasing age - also by the resulting damages of the bile backlog (inflammations, hepatic fibrosis, cirrhosis, portal hypertension, …). Longer life expectancy and the frequent intake of medication (antibiotics, steroids, theophylin, …) additionally strain the liver.
The current medical standard therapy of cholestasis in CF amounts to the prophylactic administration of ursodeoychloric acid (ADCA) in order to counteract the thickening of the bile. The treatment is carried out empirically. Data, especially on the long-term affects in CF, is insufficient (Götz 2004, Lang 2001 und Cheng et al 1999).

A proposed therapy is the osteopathic treatment of the hepatobiliary system.
Positive effects have been detected using the osteopathic treatment in asthma and diabetes patients (Marcer 2003, Wheatley et al 2000 and Jealous 1997).

Empirical experiences of the test center have shown that in almost all osteopathic treatments of the CF patients, the liver emerges as the key organ.

The osteopathic treatment methods aim at optimizing the function of the liver and the bilinear system – under consideration of reflex influences (vagus, sympathetic nervous system, segmental supply, …) and anatomical connections – for the individual patients.
From a functional point of view, the chronic bile backlog is reduced through the regular opening and drainage of the bile ducts, and thus the related, secondary failures in the area of the liver and the biliary tracts (inflammations of the liver parenchyma, liver cirrhosis, portal hypertension, gall stones, extrahepatic stenosis, …) are reduced or retarded (Helsmoortel 2002, Eisenburg 1992).

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Already in 1969, in an article of the “Almanac of selected osteopathic scientific publications", Hoover reported on the treatment of the lesion of the gallbladder described by Dr. A. T. Still (Hoover 1969).

The objective of this study is to examine the already existing treatment methods for their efficacy in CF patients.
The results gained may represent a future improvement in the treatment in the digestive area in CF patients.

In order to minimize the efforts for the patients, the study is designed in such a way that all of the medical data used is gained from the normal routine examinations.

2.2.6. Objective of the study

This pilot study shall serve to identify the influence of a 12-month osteopathic treatment series on the liver and biliary tracts in CF.
The objectives are to monitor and document changes in the condition of the patient, in the liver and bile metabolism, in the portal venous flow, in the lung functions, in the medication and in the hospital stays.

A general **working hypothesis** is assumed.

Osteopathic treatment of the hepatobiliary system leads to an improvement in the transport of bile acid. It reduces inflammation processes in the liver parenchyma and reduces abdominal pain and wind and therefore improves the quality of life for patients with cystic fibrosis.

2.2.7. Design of the study

In this prospective, randomized, monocentric, clinical study, the osteopathic treatment methods in patients with CF will be confronted with a zero therapy.

2 intervention groups:

O group: Osteopathic group
K group: Control group

In total, 18 people per group will be included (Intention-To-Treat collective).
20% drop-outs are allowed for. The objective is to have approx. 15 valid cases for efficacy per group (per protocol collective).

In addition to medical and physiotherapeutic standard therapies, the patients in the O group will receive 9 osteopathic treatments over the period of a year.

The patients in the K group only receive the medical and physiotherapeutic standard therapies.

2.2.8. Randomization

The randomization is carried out based on 2 randomization lists that have been created by statisticians and deposited in sealed envelopes by a neutral person.
2 randomization lists have been created since the patients assigned from Vienna and the Upper Austria patients have been separately randomized in order to enable a subgroup analysis. Pro Stratum Upper-Austria (List A) or Vienna (List B), a maximum of 26 cases will be calculated.

As a CRF annex (group allocation after patient inclusion), 52 envelopes (26 envelopes/stratum) will be assigned by the neutral person and it contains the respective group allocation for the O and K groups.

The envelopes will be opened after the initial examination (E1).

The sealed envelopes with the randomization lists may only be opened after the completion of the study.

2.2.9. Study participant selection

2.2.9.1. Inclusion criteria:

- After written and oral explanation, the patient shall personally sign a consent form, or in the case of a minor, at least one legal guardian shall also sign the consent form. Forms can be found in the appendix.
- Mucoviscidosis (CF)
- Pancreas insufficiency
- Age between 8 and 99 years old.
- Assumed availability within the period
- The last routine annual examination is not longer than 3 months ago.

2.2.9.2. Exclusion criteria:

- Known pregnancy
- A desire to have children in the expected monitoring period in childbearing women
- Liver cirrhosis
- Aortic aneurysm
- Liver, gall, stomach and pancreas tumors

2.2.10. Study intervention:

In addition to their previous standard therapy, the patients in the O group will receive 9 osteopathic treatments (OT) for the hepatobiliary system á 30 minutes in an interval of 6 weeks +/-2 weeks. For a "valid case", the patient must have received at least 80% of the osteopathic treatments (OTs) after 12 months.

The treatment is standardized through the use of osteopathic treatments in accordance with the international osteopathic standards.

2.2.10.1. Osteopathic Report:

A short osteopathic report is carried out before each treatment:

- **Anamnesis**
- **Visceral tests:**
    - **Inspection:** Assessment of the shape of the abdomen
    - **Acouophonia**
    - **Palpation** and Ecouté: - Tension test especially of the liver, gall bladder, abstersive biliary tracts, diaphragm, duodenum, suspending apparatus of the organs such as fascia and ligaments and the surrounding organs.
    - **Mobility test** of the organs for example during breathing
        - Aggravation and relief tests
        - Examination of the influences of the organs on each other (Fieuw et al 2005, Ligner 2005, Helsmoortel 2002, Paoletti 2001, De Coster 1995)

The description of the techniques can be found in the appendix under Detailed Description of Methods.

2.2.10.2. Osteopathic treatment:

- After a short osteopathic report, the liver and the biliary system are treated in accordance with the international osteopathic standards.
- The documentation of the osteopathic report and treatment measures of each session are recorded CRF (Case Record Form) (an example can be found in the appendix CRF).
- **The treatment package (OT) :**

    - Relaxing the diaphragm
    - Preparing the duodenum –sphincter oddi
    - Relaxing the descending bile ducts
    - Correcting the gallbladder (gallbladder drainage)
    - Improving motility and mobility of the liver
    - Liver pump
    - Other osteopathic techniques when necessary (Fieuw et al 2005, Ligner 2005, Helsmoortel 2002, Paoletti 2001, De Coster 1995)

The description of the techniques can be found in the appendix under Detailed Description of Methods.

In the event of gall stones or duodenal tube feeding, the techniques will be respectively modified.

The technique of bile drainage may not be applied for gallstones due to the danger of mobilizing the stone - otherwise there are no restraints.
In the case of tube feeding, the techniques must be carried out in such a way that no irritation or strain arises in this area.

Duration of each session: approximately 30 minutes

If necessary, the treatment may also be carried out outside of the test center.

Table 1:

Study interventions

	Standard medication	Physiotherapy Breathing therapy (Standard)	1 OT / 6W (+/- 2W) à 30min	Other medical care (Standard)
O group	X	X	X	X
K group	X	X		X

2.2.11. Accompanying measures

Accompanying measures and habits such as the medication and physiotherapy remain unchanged, but are documented as are the hospital stays.

The study team must be notified of changes in the accompanying measures and habits for the documentation.

The patients may not receive parallel osteopathic treatment beyond the study.

Otherwise, there are no restraints on the accompanying medication and all medical measures.

2.2.12. Study procedure

- **The patient recruitment** is ongoing and ends 24 months after the inclusion of the first patients in the study.

- **Establishing contact:** The referring and supervising doctor regularly examines the patients. If the patient meets the inclusion criteria, and principally shows interest in participating in the study, they are recommended and assigned to the test center.

- An appointment is made together with the patient. This is followed by a rough clarification of the inclusion and exclusion criteria.

- If the patient is eligible for the study, he/she is then informed in writing and orally about the study (This does not necessarily have to take place in the test center. It can also be done ambulatory in order to reduce the traveling times of the patients). In the event of a minor, at least one legal guardian is informed and clarified on the study at the same time. The patient has a week to consent to participation and he/she receives written patient information and a consent form for approval. The example of the patient information and the consent form can be found in the appendix.

- After a week, an appointment is again made telephonically. The possibility of assignment for the osteopathic treatment by the referring doctor is provided if necessary (for the legal coverage of the treatment, not for settlement purposes).

- Check of the inclusion and exclusion criteria.

- If the patient (and if necessary a legal guardian) signs the consent form, he/she is assigned an identification number (IDNR) and the study begins with the initial examination.

- **Initial examination (E1):**
    - Demographic data
    - Anamnesis (including questions on medication and hospital stays in the last years)
    - CFQ-R (The questionnaires on the quality of life and the related manual can be found in the appendix)
    - VAS (The visual analog pain scale can be found in the attachment)
    - Measured values of the last routine annual examination by the treating doctor such a bile acid, liver function, clotting factors, ultrasound including venous portal flow, FVC, MEC 75-25, FEV1 are consulted for the study and accepted for E1 when the values are not older than 3months (otherwise no admittance of the patient in the study).
    - Once the E1 is completed, the patients are assigned to groups.

- **Group assignment:**
    - For the group assignment, the related envelope of the inclusion sequence (Stratum A-1 to A-26, or B-1,...) is opened.
    - Once the group membership has been determined, the patient receives the respective study participant ID card (for the example, please see the appendix).

- **Intervention phase 1**
    - For the patients of the O group, the assignment from the referring doctor will be personally collected by the director of studies or by the patients themselves.
    - The patients of the O group receive the first OT additive to the medical and physiotherapeutic standard therapies, and appointments for further OTs are made. One OT is scheduled every 6 weeks (+/- 2 weeks). The patient should therefore

complete at least 2 osteopathic treatments in this phase. The accompanying measures are documented.

- The patients in the K group only receive the medical and physiotherapeutic standard therapies.

- **Intermediate examination (IE):**
  - 3 months +/- 2 weeks after E1, all patients are scheduled for an intermediate examination.
  - The patients of the O group are examined shortly before the 12 week OT.
  - IE includes:
    - Aetiopathology of the last 3 months
    - Questions regarding medication and hospital stays
    - CFQ-R
    - Visual analog pain scale

- **Intervention phase 2**
  - Every 6 weeks (+/- 2 weeks), the patients of the O group receive an OT in addition to the medical and physiotherapeutic standard therapies. A patient should complete a total (12 months after E1) of 9 x OTs. The accompanying measures are documented.
  - The patients in the K group only receive the medical and physiotherapeutic standard therapies.

- **Final examination (E2):**
  - 12 months +/-3 weeks after E1, all patients are scheduled for a final examination.
  - Those in the O group are schedule 2 to 4 weeks after the 54 week OT.
  - E2 includes:
    - Height, weight, BMI
    - Aetiopathology of the last 9 months
    - Questions regarding medication and hospital stays
    - CFQ-R
    - Visual analog pain scale

- Measured values of the last routine annual examination by the treating doctor such a bile acid, liver function, clotting factors, ultrasound including venous portal flow, FVC, MEC 75-25, FEV1 are consulted for the study and accepted for E2 when the values are not older than 3 months (otherwise Drop-out status).

- During the entire course of the study, all undesired occurrences, medication, existential orientation and side affects are documented.

2.2.13. Procedure Plan

“Osteopathic Treatments of the Hepatobiliary System in Mucoviscidosis”

Figure 2: Course of the study for a patient

				Active Phase - 12 months (+/- 3 weeks)			
		Start		Intervention phase 1 approx. 3 months		Intervention phase 2 approx. 9 months	
O group	C	E1	R	Osteop. treatment standard therapy	IE	Osteop. treatment Standard therapy	E2
K group	C	E1	R	Standard therapy	IE	Standard therapy	E2

R = Randomization E1 = Examination 1 IE = Intermediate examination

C = Establishing contact E2 = Examination 2

Total duration of study: 36 months

2.2.14. Methods

2.2.14.1. Data collection:

- **CFQ-R Austria (CF, Q**uestionnaire**):**
  - Validated questionnaires on the quality of life with respect to age are used for Austria and CF.
  - The CFQk-R Austria is conceived for children in the ages of 8-14 years. The questioning is carried out in the form of an interview and a supplementary questioning of a parent or legal guardian (CFQe-R Austria). The interviewer is the non-medical director of studies.
  - The CFQ14+R Austria is for the questioning of 14-17 year old patients and is completed by the patient themselves.
  - The CFQ18+R Austria is for the questioning of adults and is completed by the patient themselves.
  - The evaluation of the quality of life follows in "items" and a conversion factor for an evaluation scale of 1-100 (combination of CFQk-R and CFQe-R with CFQ14+R and CFQ18+R).
  - The example of the questionnaire and information for the evaluation can be found in the appendix.
- **Visual analog pain scale:**
  - A form can be found in the appendix.

The ascertainment of the CFQ-R, the visual analog pain scale and the anamnesis are conducted by the non-medical director of studies or under their supervision.

- **Laboratory values:** Blood values
  - All lab values of a patient are surveyed by the same laboratory using the same methods.
  - Clotting factors
  - Liver function
  - Bile acid

- **Pulmonary function**
  - All pulmonary function parameters of a patient are surveyed by the same department using the same methods.
  - FVC
  - MEF 75-25
  - FEV1

- **Ultra-sound**
  - The ultrasound examinations of a patient are surveyed by the same department using the same methods.
  - Descriptive ultrasound report
  - HVPG

The lab values, pulmonary function and ultrasound values are used by the treating doctor from the respective annual examinations.

2.2.14.2. Target parameters

Paramount target parameters: **Parameters from E1 and E2**

- **CFQ-R (quality of life):**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). In the case of CFQ-R, the absolute values are given in the measuring unit %.

If necessary, single chapters or items of the questionnaire will additionally be separately evaluated.

- **Visual analog pain scale:**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

- **Bile acid** in blood:

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

- **GOT (Glutamic oxaloacetic transaminase):**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

- **GPT (Glutamic pyracetic transaminase):**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

- **PTT (Partial Thromboplastin Time):**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

- **FVC (Forced Vital Capacity):**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). The measured value "FVC% of the target value" is consulted in the evaluation.

- **MEF 50**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). The measured value "MEF 50% of the target value" is consulted in the evaluation.

- **FEV1**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). The measured value FEV1 % of the VC is consulted in the evaluation.

- **Pancreas enzyme (Kreon):**

The target parameter is the change of the prescribed dose ……/kg/KG/day from E1 to E2 in absolute values and in percent.

- **Ursodeoxycholic acid (UDCA – Ursofalk):**

The target parameter is the change of the prescribed Dose ……/kg/KG/day from E1 to E2 in absolute values and in percent.

- **Hospital stays:**

The target parameter is the change in number of days spent in hospital and the number of hospital stays in the last 12 months in comparison from E1 to E2.

- **Hepatic Venous Pressure Gradient (HVPG):**

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

- **Descriptive US report:**

Categorization according to need and evaluation of the changes from E1 to E2.

Subordinate target parameters:

The following measurement parameters:

- **CFQ-R**

The target parameter is the progression from E1 to IE (absolute value – measurement unit % - and in percent E1=100%).

- **Visual analog pain scale**

The target parameter is the progression from E1 to IE (absolute value and in percent E1=100%).

2.2.14.3. Safety parameters:

- Undesired occurrences are documented.
  - Categorization according to need
  - Incidences
- Progress of BMI, body weight and body height (E1 – E2)

2.2.14.4. Group comparability parameters:

The following initial values from E1 are consulted for the group comparability:

- Demographic data (BMI, sex, age)
- Anamnesis (hospital stays, medication)
- Laboratory values
- CFQ-R
- Nutritional rating (analog scale see DRF)
- Physiotherapy (Yes / No)
- Visual analog pain scale

2.2.15. Risks

According to the experience of the test center, there are no relevant risks. All side-effects are assessed as mild and short-term and mainly manifest themselves in a possible deterioration of the patient's feelings/condition (fatigue,…) or in a increase of symptoms (diarrhea, slight stomach ache, nausea,…). A possible reaction time of 3 – 7 days is assumed.
The rare temporary epiphenomena generally correlate with the positive effects through the treatment.

2.2.16. Serious and unexpected, undesired occurrences

- **Undesired occurrences:**
  - Undesired occurrences including side-effects are documented in CRF.
  - The undesired occurrences are categorized according to need.
- **Unexpected undesired occurrences**
  - The unexpected undesired occurrences are documented in CRF and categorized according to need.

- The unexpected undesired occurrences are forwarded to the medical director of studies for inspection. The comments of the medical director of studies are forwarded together with the relevant form to the Ethics Commission and the non-medical director of studies.

- **Serious undesired occurrences**
  - Serious undesired occurrences are documented in CRF.
  - The serious undesired occurrences are forwarded to the medical director of studies for inspection. The comments of the medical director of studies are forwarded together with the relevant form to the Ethics Commission and the non-medical director of studies.

The form for undesired occurrences can be found in CRF in the appendix.

2.2.17. Ending study participation

- A pregnancy is established.
- Discovery of a erroneous inclusion
- Non-attendance of IE or E2 for longer than 1 week beyond the tolerance period.
- Withdrawal of consent by the patient.
- Loss of authority/responsibility of a patient (e.g. relocation)

2.2.18. Drop-out criteria

Drop-out criteria include serious offences against the study conditions:

- Premature ending of study participation.
- Non-achievement of 80% of OTs after 12 months.
- Gross changes in accompanying measures – at the discretion of the director of studies.
- Intake of medication with known liver-damaging side-effects – at the discretion of the director of studies.
- Noncompliance with the tolerance period.
- Non-completion of the CFQs or missing visual analog pain scale survey in E1 and E2.
- Other serious offences at the discretion of the director of studies.
- Unavailability of the routine data of the annual examination assigned to E2 (max. 3 months before E2).

2.2.19. Termination of treatment

A termination of treatment follows at the patient's request and the reasons are documented. Or, if based on medical reasons, termination is at the discretion of the medical director of studies and the non-medical director of studies (e.g. with side-effects resulting from OTs, hypertonic crisis, suspected aortic aneurysm,…). The treating doctor can also terminate the treatment.

2.2.20. Termination of the study

A termination of the study can be effectuated by the Ethics Commission, the medical director of studies or the non-medical director of studies due to medical or organizational reasons.

2.2.21. Data recording and documentation

The non-medical director of studies is responsible for the data recording, documentation and check for completeness and plausibility.

The medical and non-medical directors of studies have access to the entire patient data.

In the CRFs, the patients are entered by ID number – neither their name nor their initials are documented. Only the medical and non-medical directors of studies can assign the IDNRs to the respective patients.

The decipherment of the codes is found in two lists, one for Austria (A) and one for Vienna (B), which are stored safely by the non-medical director of studies (but which can be viewed by the medical director of studies at any time).

2.2.22. Biometric test planning and evaluation

2.2.22.1. Intention-To-Treat – Per Protocol Analysis – Missing Values

Intention-To-Treat Analysis:

In the Intention-to-treat analysis, all cases are accepted

- which have started with the OT (OT group)
- or where a period of 6 weeks has elapsed (K group).

Per-Protocol Analysis:

In the per-protocol analysis, all cases are accepted that have not been classified as drop-outs (compare Chapter Drop-out criteria).

- The per-protocol analysis is significant for the target parameters.
- The safety parameters are evaluated according to the intention-to-treat and the per-protocol principle.
- Target parameters not used in the per-protocol analysis are presented in single data listings.
- Missing values are not replaced.

2.2.22.2. Descriptive and closing statistics:

Descriptive analysis:

All of the data documented in the questionnaires (CRFs) are tabulated stating the number of observed and missing values.

Nominal variables are represented in tables with absolute and relative frequencies.
Ordinal variables are represented in tables with absolute and relative frequencies and/or by using median, quartiles, minimum and maximum.

For metric variables, the distribution of the following values is represented:

Minimum
Median
Quartile
Maximum
Average
Standard deviation
Number of cases

If necessary, box plots can be created and confidence intervals can be calculated.

Closing statistics (group comparisons):

"In the event of quantitative measurements, all parameters will be statistically analyzed using a 2-sample T test for independent random samples, whereby a possible variance heterogeneity will be considered. Should there be an extreme deviation of the data from the normal distribution (test using the Kolmogorov-Smirnov Test with Lilliefors significances, alpha = 5%), or if the data is ranked data, the Mann-Whitney test is then applied. Nominally scaled data are analyzed using the Chi square homogeneity test or Fischer's exact test. The alpha error level is set at 5% (on both sides) for each test – an adjustment of the alpha error is not made. The results of these tests are therefore to be understood as being purely descriptive. They can however be used as a basis for the case number estimates for future investigations."(Schimetta nov 2006)

2.2.22.3. Subgroup analyses:

Obligatory subgroup analyses:

A priori, the following subgroups are planned:

- For each assigning province (Upper Austria, Vienna)
- For ages ≥/<14 years (CFQe-R plus CFQ14+R; CFQk-R)

Facultative subgroup analyses:

If the patient data allow it, the following subgroup analyses are planned i.e. when the number of cases for the respective subgroup of n=6 per group (O and K) is reached:

- Bile – measured value outside of the normal range
- Visual analogue pain scale > 30
- GOT – measured value outside of the normal range
- GPT – measured value outside of the normal range
- PTT – measured value outside of the normal range
- HVPG – measured value outside of the normal range
- US – measured value outside of the normal range

- Hospital stay(s) YES

Should further interesting questions arise due to the status of the data, which can be answered by forming subgroups, a post-hoc analysis is then possible. The resulting statistic findings are however to be understood as being purely descriptive.

The above-mentioned representations and evaluation methods (descriptive and closing statistics) are used for all subgroup analyses.(Schimetta Nov 2006)

2.2.23. Administrative aspects

The recruiting shall begin after the approval by the Ethics Commission.
The recruiting phase will last 24 months after the inclusion of the first patients in the study. If not all 36 patients are included within this period, the study will be concluded with the attained number of cases.

2.2.24. Ethical aspects

The study will be conducted in total compliance with the Helsinki declaration.

Consideration of benefits and risks

The potential benefits in the O group are confronted with a practically non-existing and/or irrelevant risk.
In the K group there is no deviation from the routine.

2.2.25. Insurance

The osteopathic treatment is non-invasive and is not linked with any relevant risk, and no medical examination is carried out outside of the routine.
Insurance is thus not deemed necessary.

The existing liability insurance of the non-medical director of studies also covers the treatments for study purposes.

2.2.26. Publishing results

Publication of the results is obligatory.
As the initial author, the non-medical director of studies, Olivia Maier, is responsible for the publication. Co-authors are the medical director of studies Dr. Andreas Kainz and the statistician, Johannes Reichl, and authoritative referring doctors.

2.2.27. Responsibilities

Medical Director of Studies:

- Responsible for medical questions
- Evaluation of unexpected and serious, undesired occurrences.

Non-medical Director of Studies:

- Study management
- Study administration
- Data collection excluding lab values, US and pulmonary functions
- Data check (completeness and plausibility) and data entry
- Publication
- Osteopathic treatments

Referring doctors:

- 1. Establishing first contact with potential study participants
- Provision of measured values from the annual routine examinations and from the lab, pulmonary functions and US for E1 and E2.

Statistician:

- Planning and execution of the statistical evaluation
- Creating randomization lists

Neutral person:

- Organizing the sealed envelopes for the group allocation.

2.2.28. Appendix protocol

Detailed description of methods

Visceral osteopathy - General

"For more than a hundred years, even without a neurophysiological background, and using exact body examinations and subtle new palpation methods, American osteopaths have already been trying to evaluate palpable organs and the musculoskeletal system, as well as active and passive mobility and to interpret disorders holistically.

Changes in mobility, whether in the plus or minus area, not only manifest themselves in the structures of the musculoskeletal system. All other systems of the organism can also only then function when their proper mobility runs unhindered actively and passively." (Tilscher et al 1996, 153-154)

The lesions are sought out with the hands and one can differentiate between two types of tests:

- Ecoute Test: Tests the tension in the tissue
- Mobility test: Tests the mobility

When treating inner organs, the therapist constantly changes between induction methods and direct methods (stretching, pressure, rotation methods), whereby principally treatment is very gentle. The induction method consists of the hand sliding to a fixing position (lesion) and then maintaining a certain pressure, which can be increased slightly if needed. This results in stretching. One then returns to the initial position. Attention must be paid that the equilibrium is re-established in all three dimensions of space (Paoletti 2001).

These principles apply for all presented methods.

The osteopathic tests and the treatment package OT includes the following methods: (Individual methods will be explained in more detail)

Ecoute Test:

In the Ecoute test, the hands are placed on different sections of the body in order to perceive the movements of the body e.g. during breathing.

Ecoute Test at the lower thorax

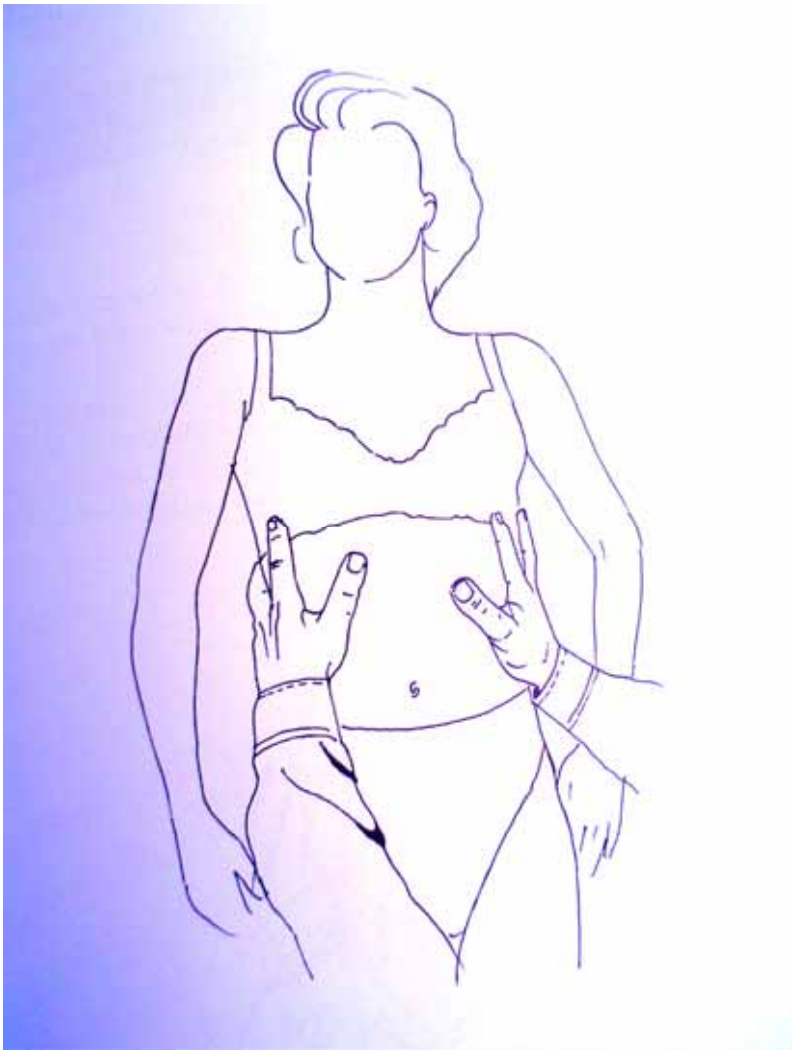

Figure 2: Ecoute at lower thorax (Paoletti 2001: 205, Fig.7.6)

The patient lies in the dorsal position (DP).

The hands lie laterally at the lower thorax. In a normal state, a harmonic movement can be felt with both hands. In the event of tension/hardening, the direction of tension may indicate the location of the lesion (Paoletti 2001).

Treating the diaphragm

See Fig. 2 General harmonizing treatment of the diaphragm

Positioning of the hands as in Point 1.

The hands trace the tension and by using induction, a tension equilibrium is established in the diaphragm.

Test and correction of the liver mobility

Fig.3 Ecoute Liver (Fieuw 2005:129, Fig.: 128)

The therapist's hands lie anterior (in front) and posterior (behind) to the liver at the lower thorax. The therapist evaluates the mobility according to amplitude and quality. The correction is made in the same position (Fieuw 2005).

Tension test and relaxation/catharsis of the ligamentum hepatoduodenale

Examination and relaxation of the tension of the fascia membrane (omentum minus) between the liver and duodenum and liver and pylorus is carried out in the same finger position. The patient is in the dorsal position.

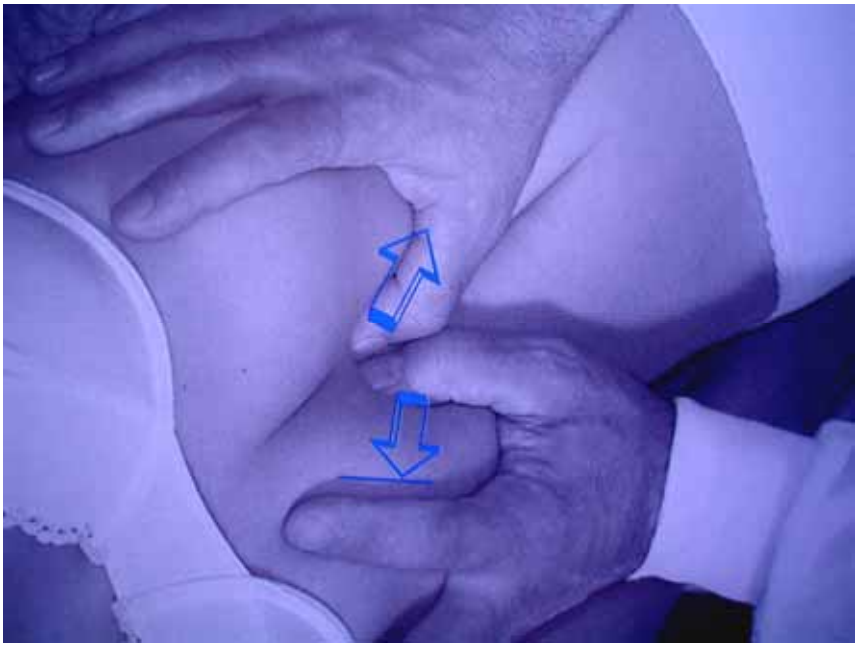

Fig. 4 Omentum minus (Fieuw 2005:30, Fig.:27)

The test:

Through the breathing, the movement of the liver to the duodenum or to the pylorus is palpated and evaluated.

The correction:

The liver is fixed using the left hand and the therapist administers the right thumb by gently pushing down and to the side in combination with the breathing (Fieuw 2005). If this method is correctly administered, it is very pleasurable for the patients.

Test and correction of duodenum 1 and 2

The test:

The tension and mobility of the duodenum is determined through a Ecoute test and palpation.

The correction:

The correction is made by stretching the duodenum or Ecoute.

Test and correction of the sphincter oddi

The test:

The tension of the sphincter oddi is directly or indirectly palpated.

The correction:

Relaxation of the sphincter oddi:

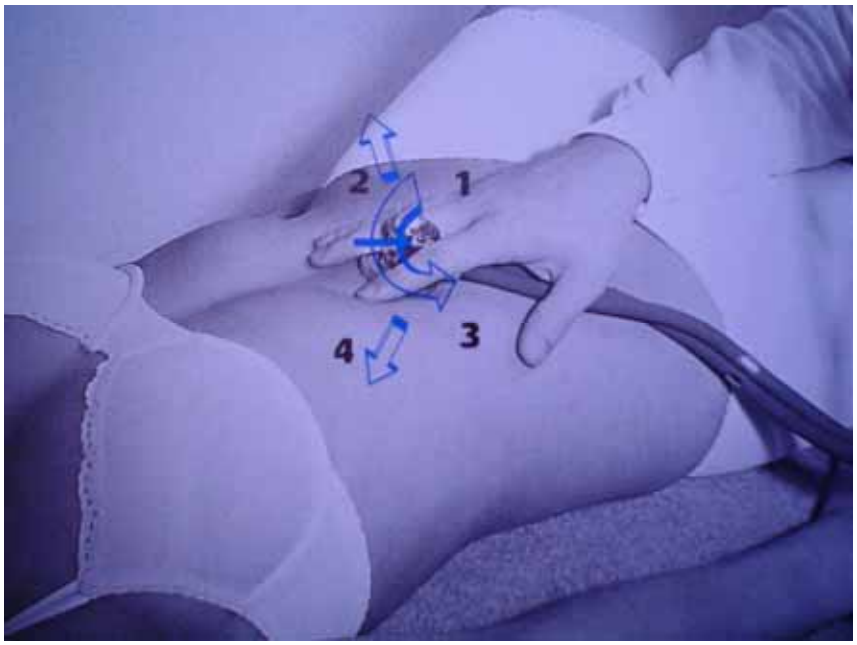

Figure.5 Relaxation of the sphincter oddi (Fieuw 2005: 60, Fig.:60)

The therapist lays their hand on the superficial projection of the sphincter oddi. They then follow the movements of the sphincter during in and exhalation with their hand. The area is treated using induction or gentle stretching until a relaxation or gurgling is observed (Fieuw 2005).

Palpation and mobility test of the liver / of the suspending system of the liver

Palpation of the liver:

Evaluation of the size and tension of the liver and/or the movements of the liver during breathing.

Palpation of the suspending system:

Evaluation of the tension of the ligaments of the suspending system.

Correction of the liver – liver pump (veno lymphatic drainage) / of the suspending system of the liver

Liver pump

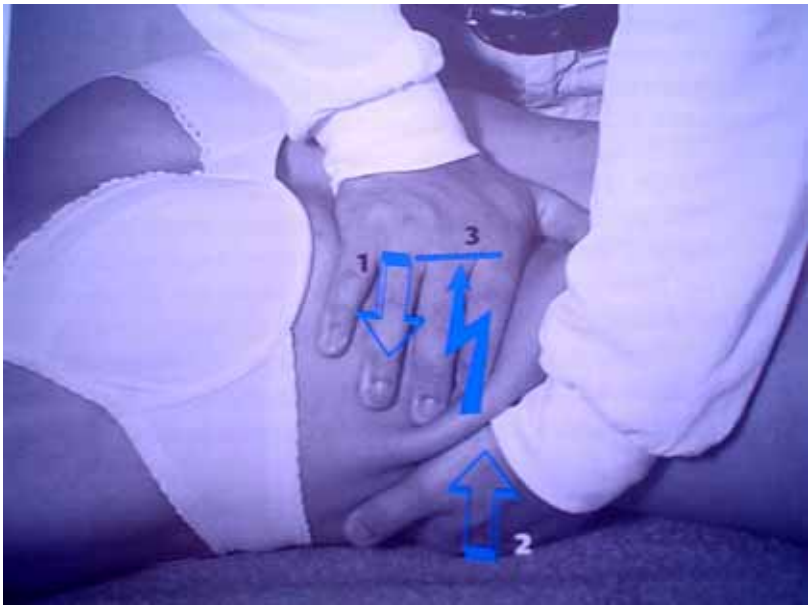

Fig. 6 Liver pump (Fieuw 2005:127, Abb.:125)

The patient breaths through her mouth. While breathing out, slight pressure is applied to the liver, which remains constant until the start of breathing in. At the end of breathing out, the pressure is suddenly released without losing contact to the skin. This results in a type of pumping mechanism (Fieuw 2005).

Correction of the suspending system of the liver:

The relaxation of the ligaments of the suspending system is carried out by stretching them.

Test and correction of the gallbladder

Test of the gallbladder:

The tension of the gallbladder and/or the pain at the site of projection of the gallbladder is palpated.

Correction:

Gallbladder drainage:

Fig.7 Gallbladder drainage (Fieuw 2005:133, Fig.:130)

The patient is seated or in the dorsal position.

The fingers of both hands are placed under the fundus of the gallbladder and the therapist tired to drain the bile liquid - starting from the fundus - to the collum (gallbladder opening). In general, patients find this method to be pleasurable.

The gallbladder drainage may not be applied for gall stones (Fieuw 2005).

Test and relaxation of the ductus choledochus (descending biliary tracts)

The test:

Palpation of the tension of the ductus choledochus.

The correction:

Relaxation of the ductus choledochus is carried out through stretching.

Other osteopathic tests and treatment methods if necessary

Since the movements in the organism occur coherently, additionally involved secondary manifestations must be noted and treated in order to prevent the automation of the pathology (Tilscher et al 1996).

Index of abbrevaitions

BMI:	Body Mass Index
CF:	Cystic Fibroses
CFQ-R Austria:	CF Questionnaire-Revised - germane version of CFQs for Austria valided
CFQk-R Austria:	CFQ-R for CF patients from 8-13 years
CFQe-R Austria:	CFQ-R for the parents from the CF patients from 8-13 years
CFQ14+R Austria:	CFQ-R for the CF patients from 14-17 years
CFQ18+R Austria:	CFQ-R for CF patients as of 18 years
CRF:	Case Report Form
FEV1:	Forced Expirations Volume in 1 second
FVC:	Functional Vital Capacity
GPT:	Glutamat-Pyramat-Transaminase
GOT:	Glutamat-Oxalat-Transaminase
HVPG:	Hepatic Venous Pressure Gradient
ICF:	Informed Consent Form
K group:	Control Group
MEF 75/50/25:	Maximal Expiratory Flow with 75%/50%/25% of vital capacity
O group:	Osteopathic Group
OT:	Osteopathic Treatment
PTT:	Partial-Tromboplastin-Time
DP:	Dorsal Position
E1:	Initial examination
E2:	Final examination
US:	Ultra Sound
IE:	Intermediate examination

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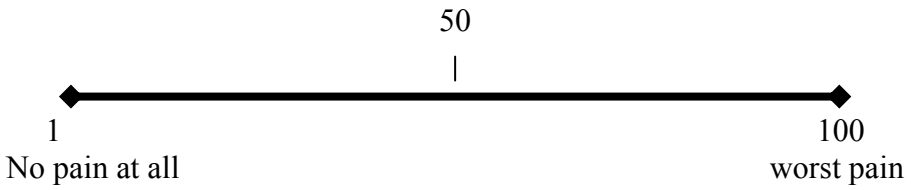
VAS

Visual analogue pain-scale

Location/Date: IDNR:

E1 / IE / E2

„How was the worst abdominal pain in the last four weeks?”



Ethic Commission

Upper Austria

Prof. Prim. Dr. Fischer

Sealed randomization list

(copy)

This envelope may only be opened after the end of the study!

2. Case Report Form (CRF)

2.2. Basic remarks

The Case Report Form (CRF) contains all patient data to be collected. Due to data protection, it is normal to only keep this under the identification number. The CRF is on one hand formally prescribed and on the other determined by the examinations required for the study. The data should be drafted considering the aspects of statistical usability, traceability of interventions, and data acquisition.

Formal prescriptions for the CRF:

- Inclusion– and Exclusion criteria
- Study interventions
- Anamneses (smokers, contraceptives...)
- Findings
- Ending study participation
- Final report
- Documentation of the treatments
- Documentation of adverse events

The form for the documentation of the “Ending study participation” and the “adverse events” are standardized.
Good and practical selection of the data to be acquired eases later statistical processing.

CRF

Case Report Form

IDNR: A-01

OT- Study:
Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses

□ O group □ K group

Test center:

Olivia Maier
Practice for Osteopathy

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3.2.1. Inclusion- and Exclusion criteria:

Inclusion criteria: please mark with a cross

- After written and oral explanation, the patient shall personally sign a consent form, or in the case of a minor, at least one legal guardian shall also sign the consent form. Forms can be found in the appendix.
- Mucoviscidosis (CF)
- Pancreas insufficiency
- Age between 8 and 99 years old.
- Assumed availability within the period
- The last routine annual examination is not longer than 3 months ago.

Exclusion criteria: please mark with a cross

- Known pregnancy
- A desire to have children in the expected monitoring period in childbearing women
- Liver cirrhosis
- Aortic aneurysm
- Liver, gall, stomach and pancreas tumors

The patient is accepted for the study: Yes / No

3.2.2. Study interventions

Study procedure

E1 – I-Phase1 (3 M. +/-2W) – IE – I-Phase 2 (12 M. +/-3W after E1) – E2

Examinations

Examinations	Intended on	Carried out on	Signature
Examination 1			
Findings 1			
Intermediate Examination			
Examination 2			
Findings 2			

Study interventions

(Only for O group patients)

Treatment	Carried out on	Signature
1. Treatment		
2. Treatment		
3. Treatment		
4. Treatment		
5. Treatment		
6. Treatment		
7. Treatment		
8. Treatment		
9. Treatment		

3.2.3. Examination 1

1. Demographic data		
ID No.	Location:	Date:
Age:	Sex: F / M	Weight: kg Height: cm BMI:
Diagnosis:		

2. Anamnesis	
2.1: Previous aetiopathology (describe): …… …… …… …… …… …… …… ……	
2.2: Smoker: Yes / No	**If yes, How many ……../day**
2.3: Pregnancy test (F): **Carried out in the last month: Yes / No**	**Comment:…….** **……**

2.4: Nutrition: Self-evaluation (1-10)

1 **10**

1=very bad nutrition, 10=very healthy nutrition

Special diet: Yes / No **If yes: Which:……..** **……** **……**	**Supplementary nourishment: Y /N** **If yes: Which:……..** **……..** **……**	**Dietary supplement (Vit.,.): Yes / No** **If yes: Which:……..** **……** **……**

2.5: Medication:

Respiration: (Permanent therapy) - Oral: …… …… …… - Inhalative:…….... …… …… ……	Digestion: (Permanent therapy) Kreon: ……prescribed dose/day Ursofalk: …….... prescribed dose/day Miscellaneous: …….. ……..	Additional medication in the last 2 months: …….. …….. …… …… …… …… ……

2.6: Hospital stays (HS) in the past year(12 months) Yes / No		
2.6.a: If yes:	Days/12 months:…….	Number of HS:……
2.7: Physiotherapy: Yes / No	Number:…… /year	

2.8:Other therapies and complementary medical measures: Yes / No

2.8.a: If yes ……Number: / year
……...Number: / year
……...Number: / year
……...Number: / year

2.9: Results

2.9.a. Laboratory:	2.9.b. Pulmonary function:	2.9.c. US:
PTT: …….	FVC: ……l, % target: ……..	……
GOT: ……	FEV1: ……l, % FC…….,	……
γGT:…….	% target:……..	……
GPT: ……	MEF50:…….l/sec,	HVPG: ……..mmHg
Date: ……	% target: …….	Date: ……
	Date: ……	.
Surveyed by:		Surveyed by:
……	Surveyed by:	……
……	……	……
	……	
2.9.d. X-ray:	2.9.e. CT:	2.9.f. Miscellaneous:
……	……	……
……	……	……
……	……..	……
Surveyed by:	Surveyed by:	Surveyed by:
……	……	……
……	……	……

2.10. Questions on digestion:
Description:……
……
…….

Stool:

□ more than twice a day □ pain during bowel movement □ hemorrhoids
□ constipation □ diarrhea □ blood in stool □ foul smelling fatty stool
□ light-colored stool □ very dark colored / black stool □ soft □ liquid □ hard □ normal □ other ……..

Urine:

□ normal □ dark urine □ haematuria □ other…….

2.11: Pain:

WHERE:	WHEN: (Frequency)	HOW:	Cause:
1)…….	1)……..	1)……..	1)……...
2)…….	2)……..	2)……..	2)……...
3)……....	3)……..	3)……..	3)……..
4)……..	4)……..	4)……..	4)……..

Please mark with a cross:	□ VAS carried out	□ After completion of E1, envelope with group assignment opened.
□ CFQ14+ carried out □ CFQ18+ carried out	□ CFQk-R carried out □ CFQe-R carried out	
□ O group □ K group □ Study participant ID handed out		Examiner/Signature:

Envelope
Randomization

A-01

Only open after Examination 1!

(Copy)

3.2.4. Intermediate Examination

1. Demographic data		
ID No.		Date:
Weight: kg	Height: cm	BMI:

2. Anamnesis
2.1: changes in aetiopathology: yes/no …… …… …… …… …… …… ……
2.4: Nutrition: Self-evaluation (1-10) **1** **10**  1=very bad nutrition, 10=very healthy nutrition

Special diet: Yes / No **If yes: Which:……..** **…….** **…….**	**Supplementary nourishment: Y /N** **If yes: Which:……..** **……..** **……**	**Dietary supplement (Vit.,.): Yes / No** **If yes: Which:……..** **…….** **…….**

2.5: Medication:		
Respiration: (Permanent therapy) - Oral: …… …… …… - Inhalative:…….... …… …… ……	Digestion: (Permanent therapy) Kreon: ……prescribed dose/day Ursofalk: …….... prescribed dose/day Miscellaneous: …….. ……..	Additional medication in the last 2 months: …….. …….. …… …… …… …… ……

2.7: Physiotherapy: Yes / No Number:……./year
2.8:Other therapies and complementary medical measures: Yes / No
2.8.a: If yes ……Number: / year ……...Number: / year ……...Number: / year ……...Number: / year

2.10. Questions on digestion:

Description:……
……
…….

Stool:

□ more than twice a day □ pain during bowel movement □ hemorrhoids
□ constipation □ diarrhea □ blood in stool □ foul smelling fatty stool
□ light-colored stool □ very dark colored / black stool □ soft □ liquid □ hard □ normal □ other ……..

Urine:

□ normal □ dark urine □ haematuria □ other…….

2.11: Pain:

WHERE:	WHEN: (Frequency)	HOW:	Cause:
1)…….	1)……..	1)……..	1)……...
2)…….	2)……..	2)……..	2)……...
3)…….....	3)……..	3)……..	3)……..
4)……..	4)……..	4)……..	4)……..

Please mark with a cross:	□ VAS carried out	Examiner/Signature:
□ CFQ14+ carried out	□ CFQk-R carried out	
□ CFQ18+ carried out	□ CFQe-R carried out	

3.2.5. Examination 2

1. Demographic data		
ID No.		Date:
Weight: kg	Height: cm	BMI:
Diagnosis: (Changes)		

2. Anamnesis	
2.1: Changes in aetiopathology in the last 9 months: Yes /No …… …… …… …… …… …… …… ……	
2.2: Smoker: Yes / No	**If yes, How many ……../day**
2.3: Pregnancy test (F): **Carried out in the last month: Yes / No**	**Comment:…….** **……**

2.4: Nutrition: Self-evaluation (1-10)

1 **10**

1=very bad nutrition, 10=very healthy nutrition

Special diet: Yes / No **If yes: Which:……..** **…….** **……**	**Supplementary nourishment: Y /N** **If yes: Which:……..** **……..** **……**	**Dietary supplement (Vit.,.): Yes / No** **If yes: Which:……..** **…….** **……**
2.5: Medication:		
Respiration: (Permanent therapy) - Oral: …… …… …… - Inhalative:…….... …… …… ……	Digestion: (Permanent therapy) Kreon: ……prescribed dose/day Ursofalk: …….... prescribed dose/day Miscellaneous: …….. ……..	Additional medication in the last 2 months: …….. …….. …… …… …… …… ……
2.6: Hospital stays (HS) in the past year(12 months) Yes / No		
2.6.a: If yes:	Days/12 months:…….	Number of HS:……
2.7: Physiotherapy: Yes / No	Number:……/year	

2.8:Other therapies and complementary medical measures: Yes / No

2.8.a: If yes: ……Number: / year
……...Number: / year
……...Number: / year
……...Number: / year

2.9: Results

2.9.a. Laboratory:	2.9.b. Pulmonary function:	2.9.c. US:
PTT: …… GOT: …….. γGT:……. GPT: …… Date: …….. Surveyed by: …… ……	FVC: ……l, % target: …….. FEV1: ……l, % FC……, % target:…….. MEF50:…….l/sec, % target: ……. Date: …… Surveyed by: …… ……	…… …… …… HVPG: ……..mmHg Date: …… . Surveyed by: …… ……
2.9.d. X-ray:	2.9.e. CT:	2.9.f. Miscellaneous:
…… …… …… Surveyed by: …… ……	…… …… …….. Surveyed by: …… ……	…… …… …… Surveyed by: …… ……

2.10. Questions on digestion:
Description:……
……
…….

Stool:

□ more than twice a day □ pain during bowel movement □ hemorrhoids
□ constipation □ diarrhea □ blood in stool □ foul smelling fatty stool
□ light-colored stool □ very dark colored / black stool □ soft □ liquid □ hard
□ normal □ other ……..

Urine:

□ normal □ dark urine □ haematuria □ other…….

2.11: Pain:

WHERE:	WHEN: (Frequency)	HOW:	Cause:
1)…….	1)……..	1)……..	1)……...
2)…….	2)……..	2)……..	2)……...
3)……....	3)……..	3)……..	3)……..
4)……..	4)……..	4)……..	4)……..

Please mark with a cross:	□ VAS carried out	□ CFQ14+ carried out
□ CFQk-R carried out	□ CFQe-R carried out	□ CFQ18+ carried out
□ Results incomplete	□ Results complete	Examiner/Signature:

3.2.6. Ending study participation

□ **Ending study participation:** **Date:**
Reasons: …… …… …… ……
□ **Application of drop-out criteria:** **Date:**
Reasons: …… …… …… ……
□ **Study intervention termination:** **First date:** **Second date**
Reasons: …… …… …… …… ……
□ **Deviation from study conditions:** **Date:**
Reasons: …… …… …… …… …… ……..
Check: **Date:……Signature:……**

3.2.7. Final report

Evaluation of the case:
Description: (Efficacy, Tolerability) …… …… …… …… …… …… …… …… …… …… …… …… …… …… …… …… …… …… ……
Ending of study participation on:……
I confirm the accuracy of the information. Date/signature of the non-medical director of studies: ……

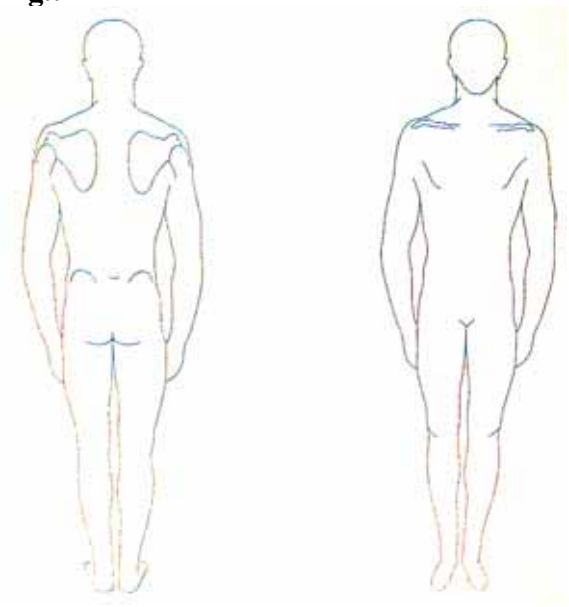
3.2.8. Treatment Report

(OT group)

Treatment No.: ……ID No.: ……
Date: …….....

Findings:

Fig.:



Findings:
……
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Safety tests: ……
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Treatment hypothesis:
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Carried out measures:
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……

Remarks:
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……
……

Signature:……

3.2.9. Adverse events:

Time / Date:
Date of the first occurrence:…… Time:…….
Duration:……..min, and/or …….hours, and/or ……..days
Clinical symptoms: Yes □ No □
Description: …… ……
Pathological lab results: Yes □ No □
Measured values: …… ……
Presumed cause: …… …… ……
Actions taken: Yes □ No □
Description: …… ……
Outcome: Subsiding □ Stable disease □ Progressive disease □ Exitus □
Classification: □ unexpected adverse event □ severe adverse event □ neither unexpected/severe adverse event □ presumable side-effect Yes ○ No ○

Comment:
…… …… …… …… …… …… …… ……

4. Application

4.1. Basic remarks

The application is drafted on the basis of the study record.
The form for the official application for the ethics commission can be downloaded from the Internet on the respective page.

As the form are primarily aimed at the submission of drugs and a great deal of expertise is assumed, in my opinion a specialist must also be involved here to avoid formal errors.

4.2. Application – Final Version

It is obligate to use the last version form

4.2.1. General:

Title of the project:

Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses

Protocol number/-short form: OT-Study

Date of the protocol: 4 October 2006

Contact: Olivia Maier, Practice for Osteopathy , Pfeffergasse 20/1, 4600 Schleißheim

4.2.2. Data of the Study

Kind of study:

○ **miscellaneous, please specify:** osteopathic study

Area: internal medicine, paediatrics

Other study centers: No

Other votes of any Ethic Commissions: No

Planned study participants: 36

Description of study participants:

Age*:* 8 – 99 Years

Are persons included who are not able for personal consent? No

Included: female and male participants

Are fertile women included? Yes

Duration of the participation for each study participant:

Active phase*:* 12 months

Duration of the study total: 36 months

4.2.3. Insurance

An Insurance is needed: No

4.2.4. Specification about treatment and diagnose

Following treatments and measurements will be carried out solely for study purposes:

Kind	Quantity /Dose	Time	Total
Osteopathic treatment	1/6 weeks (+/- 2 w) á 30 min	12 months	9
CRQ-R	1x at the beginning, 1x after 3 months, 1x at the end	12 months	3
VAS	1x at the beginning, 1x after 3 months, 1x at the end	12 months	3

Following measurements (Only invasive or radiation exposed) are carried out routinely:

Kind	Quantity/Dose	Time	Total
Blood withdrawal	1x at the beginning, 1x at the end	12 months	2

4.2.5. Summary of the project

Original study title :

Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses.

Summery of the project:

Cystic fibrosis (CF) is the most common genetically-inherited, autosomal recessive disease of the Caucasian population. The typical CG mucous obstructs the gallbladder and pancreas and prevents the digestive enzymes and bile from reaching the duodenum and the small intestine in order to help break down and digest the food. The consequences of the bile backlog secondarily result in inflammations of the liver parenchyma, and thus in typical fibrotic transformation of the liver and liver cirrhosis.

Liver disease is the cause of 5% of the deaths of CF patients (Eisenburg 1992; Lang 2001; Götz 2004).

CF patients often suffer from abdominal pain (Claaß et al 2004), wind, foul-smelling stools and maldigestion.

This pilot study shall serve to identify the influence of a 12-month osteopathic treatment series on the liver and biliary tracts in CF.

Design of the study:

Open, monocentric, controlled, randomized pilot study in parallel group design.

Study participants:

In total, 36 patients will be included (Intention-To-Treat by lot).
18 patients per group (20% drop-out quote - approx. 15 valid cases for efficacy per group in per protocol collective).

2 intervention groups:

O group: Osteopathic group – in addition to

Medical and physiotherapeutic standard therapies, they receive osteopathic treatment.

K group: Control group – receive medical and physiotherapeutic standard therapies.

Study procedure:

- Establishing contact through the referring doctor
- Determination of the inclusion and exclusion criteria
- Obtaining the consent of the patients
- Initial examination E1
- Randomization
- Intervention phase 1
- Intermediate examination IE (3 months after E1 +/-2 weeks)
- Intervention phase 2
- Final examination E2 (12 months after E1 +/-3 weeks)

Results of pre-clinical tests or reasons to abandon pre-clinical tests:

Studies with asthmatic and diabetic patients and the empiric experience of the test center have shown efficacy of osteopathic treatment. Therefore no pre-clinical tests.

Primary hypotheses of the study:

Osteopathic treatment of the hepatobiliary system in CF leads to an improvement in the transport of bile acid. It reduces inflammation processes in the liver parenchyma and reduces abdominal pain and wind and therefore improves the quality of life for these patients.

Relevant inclusion- and exclusion criteria:

Inclusion criteria:

Cystic fibrosis

Age 8 -99 years old

Pancreas insufficiency

Personal consent (& consent of a legal guardian)

Last annual examination by the treating doctor may not be older than 3 months

Availability

Exclusion criteria:

Liver cirrhosis

Aortic aneurysm

Liver, gall, stomach and pancreas tumors

Known pregnancy

Desire to have children in the treatment period in childbearing women

Ethical aspects (benefits/risks correlation):

The potential benefits in the O group are confronted with a practically non-existing and/or irrelevant risk.

In the K group there is no deviation from the routine.

Reasons for including protected groups:

CF- is a hereditary disease that shortens life-time; therefore most expected patients for the study are minors. By the way the experience of the test center has shown that children have a better compliance. Hence minors are included.

Description of Recruitment:

The referring and supervising doctor regularly examines the patients. If the patient meets the inclusion criteria, and principally shows interest in participating in the study, they are recommended and assigned to the test center.

Procedure of the study center to inform patients about the study and to get the consent of the study participants, and respectively the parents or a legal guardian):

In the first interview the patients and in case of minor at least one legal guardian are informed in writing and orally about the study. They then have one week to consent to participation and they receive written patient information and a consent form for approval (ICF in the appendix). After a week, an appointment is again made telephonically. The consent has to be signed by the patient himself and in case of minor additionally by one legal guardian (different forms see study protocol).

Risks

According to the experience of the test center, there are no relevant risks. All side-effects are assessed as mild and short-term and mainly manifest themselves in a possible deterioration of the patient's feelings/condition (fatigue,…) or in an increase of symptoms (diarrhea, slight stomach ache, nausea,…). A possible reaction time of 3 – 7 days is assumed. The rare temporary epiphenomena generally correlate with the positive effects through the treatment.

Estimated advantages for included participants:

Through the application of osteopathy, Quality of life may possibly be improved. Especially improvements in stomach pains, wind, diarrhea, constipation and other digestive problems are possible.

Relation participant / tester:

Patient - Osteopath

Methods to find and document unexpected effects:

In the Examinations E1, IE, E2 and before each treatment the patient will be asked by lists and orally questions about their well being and reactions of the treatments. All will be documented. If adverse events occur, they will be documented in the expected forms and from the medical director classified. In case of severe and unexpected adverse events the ethic commission will be informed.

Methods to protect personal data of the participants (additional to point 5.):

The lists with names and corresponding ID-numbers are on hands by the non-medical director.

Planed prevention for the persons after participation in the study:

If a further osteopathic treatment is necessary it will be arranged by the non-medical director.

Refunding or compensation for the participants:

Study participants reimburse travel expenses of € 1.20 - per 10 km. Participants of the K group receive 2 osteopathic treatments after their participation free of charge.

Rules for termination of the study:

A termination of the study can be effectuated by the Ethics Commission, the medical director of studies or the non-medical director of studies due to medical or organizational reasons.

Funding of the study or other interests of the directors:

This study is part of the Master Theses of the Non-medical director of studies and she is the founder of the Study.

4.2.6. Biometrics, data protection

Study design:

open, controlled, randomized, monocentric pilot study in parallel group design.

Number of groups: 2

Stratification: Yes **criteria:** federal states

Repetition of measures: No

Main target parameter:

Because of the character of a pilot study there are only paramount target parameters.

Paramount target parameters: **Parameters from E1 and E2**

CFQ-R (quality of life):

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). In the case of CFQ-R, the absolute values are given in the measuring unit %.

If necessary, single chapters or items of the questionnaire will additionally be separately evaluated.

Visual analog pain scale:

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

Bile acid in blood:

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

GOT (Glutamic oxaloacetic transaminase):

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

GPT (Glutamic pyracetic transaminase):

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

PTT (Partial Thromboplastin Time):

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

FVC (Forced Vital Capacity):

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). The measured value "FVC% of the target value" is consulted in the evaluation.

MEF 50

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). The measured value "MEF 50% of the target value" is consulted in the evaluation.

FEV1

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%). The measured value FEV1 % of the VC is consulted in the evaluation.

Pancreas enzyme (Kreon):

The target parameter is the change of the prescribed dose ……/kg/KG/day from E1 to E2 in absolute values and in percent.

Ursodeoxycholic acid (UDCA – Ursofalk):

The target parameter is the change of the prescribed Dose ……/kg/KG/day from E1 to E2 in absolute values and in percent.

Hospital stays:

The target parameter is the change in number of days spent in hospital and the number of hospital stays in the last 12 months in comparison from E1 to E2.

Hepatic Venous Pressure Gradient (HVPG):

The target parameter is the progression from E1 to E2 (absolute value and in percent E1=100%).

Descriptive US report:

Categorization according to need and evaluation of the changes from E1 to E2.

further target parameters:

CFQ-R

The target parameter is the progression from E1 to IE (absolute value – measurement unit % - and in percent E1=100%).

Visual analog pain scale

The target parameter is the progression from E1 to IE (absolute value and in percent E1=100%).

Drop-out-quote: 6 (20%)

Planned statistical analysis:

Population: Intention-to-treat; per protocol

Interim analysis: No

Statistical methods:

In the event of quantitative measurements, all parameters will be statistically analyzed using a 2-sample T test for independent random samples, whereby possible variance heterogeneity will be considered. Should there be an extreme deviation of the data from the normal distribution (test using the Kolmogorov-Smirnov Test with Lilliefors significances, alpha = 5%), or if the data is ranked data, the Mann-Whitney test is then applied. Nominally scaled data are analyzed using the Chi square homogeneity test or Fischer's exact test. The alpha error level is set at 5% (on both sides) for each test – an adjustment of the alpha error is not made. The results of these tests are therefore to be understood as being purely descriptive. They can however be used as a basis for the case number estimates for future investigations.

Data management:

Data qualification examination:

Completeness and plausibility check by the non-medical director.

Data management:

Data management by the non-medical director.

Data protection:

Data handling results only oblique on persons.

The way of anonymisation:

In the CRFs the patients are managed with an ID-number. Neither names nor initials will be adhered only the non-medical director is able to assign the ID to the concurrent patient.

5. Informed Consent Form (ICF)

5.1. Basic remarks

The ICF (Informed Consent Form and Declaration of Consent) are forms prescribed by the ethics commissions which are adapted to the study.

For studies involving minors, appropriate forms must be used for each age group resp. for the parents/guardians.

In the case of participation of minors is it desirable that the child itself and a parents/guardian sign the declaration of consent for participation in the study.

The respective form can be downloaded at www.Ethikkommissionen.at/Formulare.

5.2. The ICF – Final Version

5.2.1. Inform Consent Form 18+

Patient Information and Consent Form
for Participation in the Clinical Study

Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses

Dear Patient,

I would like to invite you to participate in the above clinical study. An extensive discussion will be held to provide you with more information on the study.

Participation in a clinical study is voluntary and can be ended by yourself at anytime without specifying any reasons and without resulting in any disadvantages in your medical or physiotherapeutic treatment.

Clinical studies are necessary to obtain reliable new medical or osteopathic research results. However, an essential prerequisite for the execution of a clinical study is that you state your consent for the participation in this clinical study in writing. Please carefully read the following text which is complementary to the informative discussion with your therapist (director of studies) and do not hesitate to ask any questions.

Please sign the consent form only

when you have completely understood the type and procedure of the clinical study,

when you are prepared to consent to participation and

when you are fully aware of your rights as a participant in this clinical study.

The responsible Ethics Commission has already approved and endorsed this clinical study, as well as the patient information and the consent form.

What is the purpose of this clinical study?

The purpose of this clinical study is to test and document osteopathic treatment methods for their effectiveness in liver and gall problems which result from your illness. Similar to

the breathing therapy, regular drainage of the of the bile from the biliary tracts reduces the backlog in the liver and thus minimizes the basis for consequential damages such as digestion problems, liver cirrhosis, etc. and with it improves the quality of life for patients with CF.

What other treatment possibilities are there?

To treat this disease, **there is also** the following possibility: The intake of ursodeoxycholic acid (Ursofalk).

What is the procedure of the clinical study?

This clinical study is executed in Upper Austria and in Vienna, and a total of 36 patients will participate.

Before being accepted into this clinical study, you should already have had your annual examination at your treating doctor. The values of the pulmonary function, the ultrasound of the liver as well as the blood values for the liver function and the bile acid are required for the study. Examinations that are a maximum of 3 months old are accepted for the examination. If you take part in the study, you give your consent for your medical history to be viewed for study purposes, and it would be advantageous if you yourself bring your information with you for the first examination.

After being accepted for this clinical study, the history of your illness will be surveyed. A questioning on demographic data, medication, hospital stays and pain will be carried out. You will then receive a questionnaire on your quality of life.

After the **first examination**, the following groups will be assigned. For this clinical study, 2 groups are intended; one osteopathic group and one control group. The group to which you will belong is decided by the director of studies opening a sealed envelope. This envelope contains the code of your group assignment.

The osteopathic group (O group) receives 9 osteopathic treatments of the liver and biliary tracts, once every 6 weeks (+/- 2 weeks) over 12 months in addition to their normal medical and physiotherapeutic therapies. The duration of the therapy is approximately 30 minutes per session. The director of studies collects the assignment/transferal for the treatments from your referring/treating doctor.

The control group (K group) continues to receive the normal medical and physiotherapeutic standard therapy that they have received up until now.

An intermediate examination is intended for all patients 3 months (+/- 2 weeks) after the initial examination and includes general questions on the aetiopathology of the past 3 months, questions on medication, questions on pain and the questionnaire on their quality of life.

The final examination for patients of both groups is held 1 year (+/- 3 weeks) after the initial examination. By this time you should have had your annual routine examination (pulmonary function, US, blood values) at your treating doctor. Examinations that are a maximum of 3 months old are accepted for the examination. The aetiopathology, the medication of the last 9 months and/or the hospital stays and pains are surveyed and you again receive a questionnaire on your quality of life.

Your participation in this clinical study will thus take approximately 12 months.

The examinations and interventions in the course of your routine examination - whether you partake in this clinical study or not - will be discussed with you by your doctor in the course of the standard medical informative discussions.

The following measures will be carried out solely for study purposes:

During the clinical study, *after 3 and 12 months*, the following examinations will be carried out by the director of studies: Surveying of information on medication, hospital stays, pain and a questionnaire on your quality of life. The patients of the O group additionally receive 9 osteopathic treatments, whereby the first and third treatment is carried out after the initial examination and after the intermediate examination respectively. For the patients of the O group, the final examination takes place 2-4 weeks after the final treatment. You are kindly requested to visit the practice for this examination. For the patients in Vienna, the location of treatment and examination will be agreed upon together with the patient. In total, 3 visits and/or 10 visits are necessary. Adherence to the visit appointments, as well as to the instructions of the director of studies, is of decisive importance for the success of this clinical study.

What is osteopathy?

Osteopathy is a philosophy and a science.

The osteopath deals with lesions or function disfunctions in the body, such as in the bones, joints and organs etc.
Through gentle, manual techniques, the osteopath attempts to remedy these dysfunctions in order to optimize the function of the affected body part.

What are the benefits of participating in the clinical study?

Through the application of osteopathy, your ailment may possibly be improved. Especially improvements in stomach pains, wind, diarrhea, constipation and other digestive problems are possible. The treatment can also positively affect the entire energy balance. It is however also possible that you do not obtain any direct benefits for your health by participating in this clinical study.

The results of this clinical study should contribute to finding a treatment for other patients that have the same disease as you.

Are there any risks, discomfort and epiphenomenon?

Through the treatment with osteopathy, it may be possible for short-term and consistently slight side-effects or reactions to arise. The side-effects and reactions observed to date include temporary diarrhea, slight stomach cramps, fatigue and nausea. A reaction period of 3 – 7 days is possible.

Does the participation in the clinical study have any other impacts/influences on the lifestyle and which responsibilities arise as a result of which?

During the participation, you should not receive any osteopathic treatment outside of the study. Otherwise there are no limitations.

What should I do in the event of symptoms, epiphenomenon and/ or injuries?

If through the course of the study, you experience any symptoms, epiphenomenon or injuries, you must inform your referring doctor and the director of studies (therapist) of such. In the event of severe epiphenomenon, please contact them immediately (if necessary by telephone). Please see below for contact telephone numbers**.**

Information for fertile/child-bearing women – pregnancy test

Pregnant women may NOT participate in this clinical study.

As a fertile/child-bearing woman, you may only participate in the study (when you are in the osteopathic group),

When a doctor determines the non-existence of a pregnancy (pregnancy test) before and once every month during the clinical study. It is additionally recommended to conduct a pregnancy test upon completion of the study.

When you commit to practice a reliable type of contraception (pill, spiral) throughout the duration of the study.

Should you however become pregnant during the clinical study or suspect that you are pregnant, please immediately inform the referring doctor and the treating therapist (director of studies).

In this case you will be kindly requested to obtain verification of the pregnancy from a doctor. The director of studies will then terminate your participation.

When is the clinical study prematurely terminated?

You may at any time recall your willingness to participate without stating any reasons, and you may withdraw from the clinical study, without resulting in any disadvantages in your medical or physiotherapeutic care.

The director of studies will immediately inform you of all new findings that are established in this clinical study and which could be of importance to you. Based on this, you can rethink your decision on the **future** participation in this clinical study.

It is however possible that the director of studies or the medical director of studies decides to prematurely terminate your participation in the clinical study, without having previously obtained your consent. The reasons for this could be:

You may not match the requirements of the clinical study;

Your treating therapist has the impression that your participation in the clinical study is not in your interests;

The medical director of studies decides to termination the entire clinical study, or to prematurely terminate only your participation.

How is the information collected in the course of this clinical study used?

In so far as not otherwise specified by the law, only the director of studies and the medical director of studies have access to the confidential information in which you are stated by name. These people are bound to professional discretion.

The distribution of data nationally and internationally is only for statistic purposes and, without exception; you will not be stated by name in this data. You will also not be stated by name in any publications of the data of this clinical study.

Are there any costs for the participants? Is there a cost reimbursement or compensation?

There are no additional costs for your participation in the clinical study.

For your participation in this clinical study, you will receive compensation in accordance with the following conditions:

Upon completion of your study participation, travel expenses of € 1.20 - per 10 km will be reimbursed.

Possibility of discussing further questions

For further questions in connection with this clinical study, the treating therapist (director of studies) and the medical director of studies will be happy to help you. Questions that deal with your rights as a patient and participant in this clinical study will also be gladly answered.

Director of studies (treating therapist): Olivia Maier

Graduate Physiotherapist and Osteopath

Available at all times under: +43 650/2076560

Medical Director of Studies: Prim. Dr. Andreas Kainz

Available at all times under: + 43 1/40180-1550

Should other treating doctors be informed of the participation in the clinical study?

It is important to also inform your treating and referring doctor.

Consent form

Name of the patient in block letters: .....

Birth date: .....

I agree to participate in the clinical study for osteopathic treatments of the liver and biliary tracts in CF.I have been extensively and clearly informed by Ms. Olivia Maier about the treatment, possible impacts and risks, as well as the nature, importance and consequences of the clinical study, and the resulting responsibilities for myself. In addition, I have read the text of this patient information and consent form, which covers a total of 9 pages. My arising questions have been comprehensibly and sufficiently answered by the director of studies. I have had sufficient time to make a decision. I currently have no further questions. I will obey the regulations that are necessary for the execution of the clinical study, yet reserve the right to terminate my voluntary participation at any time, without resulting in any disadvantages in my medical or physiotherapeutic care.

At the same time I agree that my information established in the course of this clinical study may be recorded. In order to check the correctness of the data recording, officials of the responsible state agency may, together with the medical director of studies and director of studies, view my personal illness information. When dealing with the data, the regulations of the data protection act will be noticed.

I have received a copy of this patient information and consent form. The original remains with the director of studies.

.....

(Date and signature of the patient)

.....

(Date and signature of the director of studies)

5.2.2. Inform Consent Form for Children Older than 8 Years

Osteopathic Treatment of the Liver and Biliary Tracts in Cystic Fibroses

Dear Patient,

As you know, you have a disease called “cystic fibrosis“ which restricts your digestion. You take medication for this disease.

You are invited to participate in a study, in which an osteopathic treatment method for the improved treatment of digestion problems will be investigated.

The treatment which you will receive includes gentle hand holds / grips that are mainly carried out on your stomach while you lie on the treatment bed. The treatments last about 30 minutes and are carried out every 6 weeks, for 1 year.

In order to determine how good the treatment is, there will be two groups. One group receives osteopathic treatment (O group) in addition to the previous treatments, and the other group continues to receive their normal therapy from their doctor and physiotherapist - only without osteopathy (K group).
You will only be randomly allocated to a group after your first examination.

Please read all of the information very carefully before you decide whether you want to participate in this study. Discuss it with your parents and ask your therapist (or your doctor) any questions that you are not sure of.

If you do not want to participate, you will continue to be treated as you were before.

WHAT HAPPENS TO ME WHEN I PARTICIPATE IN THE STUDY?

You have probably already had you annual examination at your doctor. I am allowed to obtain the results from your doctor or your parents will bring them along with them to the first examination.

During our first meeting, I will ask you some questions about yourself and about your illness, I will also ask you and your parents to complete a questionnaire on how you feel.

This questionnaire will be repeated with all patients after 3 months and after 1 year.

Once the first examination is over, you will be assigned to the O or K group by choosing a lot (an envelope is opened).

If you are in the osteopathic group, you will receive an osteopathic treatment from me every 6 weeks for a year.

If you are in the control group you just carry on as you did before and we will only see each other for the questioning.

Your parents will receive € 1.20 per 10 km as travel expenses.

WHAT DO I HAVE TO DO?

If you want to participate in this study, you should keep the appointments.

You should also not be treated by another osteopath outside of this study.

During your visits please tell me how you are feeling and also if anything has changed in your therapy.

WHAT DISCOMFORTS COULD THERE BE?

The osteopathic treatments can have side-effects.
They are mostly only slight and don't last very long, like for example diarrhea, slight stomach cramps, nausea or you may feel a bit tired.
However it can also be that you feel good and that you do not have any side-effects.

WHAT BENEFITS DO I GET FROM IT?

The osteopathic treatments can be very beneficial to your health. If you often have stomach ache and wind, the treatment may improve your discomfort.
Also, by participating in this study, you will be helping to treat other children with CF better in the future.

DO I HAVE TO PARTICIPATE IN THIS STUDY?

You are free to choose whether you want to participate in this study.

WRITTEN CONSENT

I have read this information and understand what this osteopathic study is about. I have discussed this with my parents and have asked the therapist (and my doctor) all the questions I was not sure of.

I am voluntarily taking part in this study and I know that I can drop out of the study at any time, without having to say why and without then receiving worse medical or physiotherapeutic care.

PATIENT

First Name _____ Surname _____

Signature _____ Date _____

NON MEDICAL DIRECTOR OF STUDIES (THERAPIST)

First Name _____ Surname _____

Signature _____ Date _____