Patient Information Sheet and Informed consent form

Study title: Efficacy of Twin Precision treatment in patients with Nonalcoholic fatty liver disease (NAFLD and NASH) - a multicenter, open label, parallel arm, randomized controlled trial

Principal Investigator:
Site name:

Sponsor: Twin Health, Bengaluru, Karnataka 560043

Introduction

Dear Ms/Mr/Mrs,

You are being invited to take part in this study that involves assessment of personalized diet-based treatment (called as Twin Precision Treatment or TPT) for patients with liver disease (NAFLD/NASH). Your participation in this study is completely voluntary and it will not have any negative impact on the treatment given to you. If you have any questions, you can contact the study doctor whose contact details are given in this document.

NAFLD is a form of liver disease which is characterized by deposition of fat in the liver (not related to alcohol intake). Patients with NAFLD usually do not have any complaints and are often diagnosed based on incidental findings like USG done for other reasons or elevated liver enzymes in blood tests. NAFLD can progress to a condition called NASH (diagnosed by liver biopsy). Currently there are no approved treatments for either NAFLD or NASH. Treatment is largely based on lifestyle modifications, reducing body weight, and controlling blood sugar level. However, the same dietary approach may not be effective and acceptable by all individuals.

Twin Precision Treatment is a personalized form of dietary intervention based on data collected from individuals using sensors and analyzed using computer technology.

The purpose of this study is to study the effect of personalized diet-based treatment (TPT) along with standard treatment in reducing the progression of NAFLD/NASH.

You will be screened for eligibility by doing blood tests and scan (MR Elastography). details about your current health condition will be collected and details about your diet, glucose control, physical activity, duration of sleep, weight, heart rate will be monitored using smart watch for 2 weeks (called as run-in period)

Patients above 18 years of age with a diagnosis of NAFLD (including NASH) will be eligible for the study. Those with comorbidities such as diabetes, hypertension (under control), obese individuals are also eligible.

Liver disease due to other condition, alcohol abuse, presenting complications related to liver disease, abnormal liver function based on blood tests, clinically significant heart disease,

malignancy, pregnant women, participating in any other clinical trial, planning for bariatric surgery (surgery for weight loss), having significant weight loss recently etc

After this you will be randomly assigned to any of the 2 groups, i.e either Twin Precision Treatment (TPT) along with standard care group or standard care only group. This will be done by a process called randomization performed using computer (like tossing a coin for heads or tails). You have equal chance of being assigned to either of the treatment groups.

Twin precision treatment with standard care group

If you are assigned to the TPT group, you will get the along with few life style modifications personalized to you. This includes providing optimal combination of macronutrients, micronutrients, and microbiome, while simultaneously guiding individual patients to avoid foods that cause blood glucose spikes and to replace them with foods that do not produce glucose spikes.

Nutritional counselling will be provided by expert post graduate well trained health coaches through the app and via telephone. You will be asked to cover 10000 steps per day (Fitbit sensor) and resistance exercises and breathing exercises. Sleep will be monitored (Fitbit sensor) and you will be counselled to get at least 7 hours of sleep.

Use of sensors and TPN app: To provide personalized diet, we will be collecting the information through sensors

- Blood sugar response to different foods (collected using continuous glucose monitoring patch)
- Change in blood pressure, heart rate, body composition via Fitbit sensors connected to the mobile app via Bluetooth
- Entering food intake into the Twin App every day

Standard care group

Lifestyle change will be focused on weight loss achieved by physical activity (aerobic activities and resistance training) and healthy diet. Participants will be encouraged to achieve approximately 7% -10% weight loss. Energy restriction will include a low calorie (1200-1600 kcal/d), low fat (less than 10% of saturated fatty acid), low carbohydrate diet (< 50% of total kcal). You will be advised physical activity (including aerobic activity and resistance training) for approximately 150 to 200 min/ week over 3 to 5 sessions.

Patient coach: You will be assigned a coach who will guide you on the diet and physical activity. You will be given a study diary where you can enter the details related to your diet and physical activity.

Standard care medications: Since there are no approved medications for NAFLD/NASH no drug will be given as part of standard care for treating NAFLD/NASH. However, management of comorbid conditions such as diabetes, hypertension will be as per routine hospital practice based on guidelines.

a. Duration of the study and number of participants

Approximately 200 NAFLD participants including those with NASH will be enrolled from different hospitals across India. The total duration of the study will be for 2 years and 6 months with 2 years of intervention followed by 6 months of only follow up.

3. What is being expected?

You will be asked to follow lifestyle modifications and diet modifications depending on your group. You will be contacted by a diet coach who will advise you on this. You will also be followed monthly in the beginning for 6 months followed by every 3 months till the end of the study. During the follow up you will be asked questions about your well-being, medications, any adverse effects along with investigations.

Patients in the TPT group will be asked to wear a Fitbit wrist band throughout the study period.

If you're assigned to the control group you will be provided with expert consultation every 3 months.

What investigations will be done during the study

Details of the investigation	**Frequency**
Blood test for hepatitis B and C, Ceruloplasmin	Baseline
Blood test for ● Blood sugar, lipid profile, insulin ● Liver function test ● Renal function test ● Thyroid profile ● Complete blood count ● Markers of Inflammation and fibrosis ● Vitamins, iron ● Exploratory markers	Baseline followed by every 3 months
Questionnaire about alcohol consumption and symptom improvement (AUDIT, NAFLD-CLDQ, EQ-5D)	Baseline followed by every 3 months
MR Elastography	Baseline followed by every 6 months till end of study
Transient Elastography	Baseline followed by every 3 months till end of study
Stool sample for microbiome assessment	Baseline, 1 month, 3 months , 1 year and post treatment followup

Details collected from sensors

- Continuous glucose monitor: Abbott Libre Pro CGM Diabetes Sensor. CGM data will be collected continuously during the first 6 months followed by once (14 days data) every quarterly.
- Systolic and Diastolic BP: Blood Pressure Monitor TAIDOC TD-3140
- Body composition parameters like weight, visceral fat, muscle mass, bone mass: Powermax BCA-130 Bluetooth Smart Scale
- Resting heart rate (RHR), step count: Fitbit charge 2 wristband
- Sleep parameters: Fitbit charge 2 wristband

*****Resting heart rate, sleep parameters only for patients in the TPT group

MR Elastography (MRE)

What is MR Elastography (MRE) ?

MR elastography is an MRI based technique to measure fat content and stiffness of the liver (important for diagnosis and treatment of patients with NAFLD). It is a safe and non-invasive scanning procedure. MRI machines are large, tube-shaped magnets.

How is it done?

During this scan you will be asked to lie inside the MRI machine. The MRI machine looks like a long narrow tube that has both ends open. You will lie down on a movable table that slides into the opening of the tube. A technologist will monitor you from another room. You can talk with the person by microphone. If you have a fear of enclosed spaces (claustrophobia), you might be given a drug to help you feel sleepy and less anxious. Most people get through the exam without difficulty.

Preparation for MRE

Before an MRI exam, you can eat normally and continue to take your usual medications, unless otherwise instructed. You will typically be asked to change into a gown and to remove things that might affect the magnetic imaging, such as: Jewelry, Hairpins, Eyeglasses, Watches, Dentures, Hearing aids, Cosmetics that contain metal particles etc.

Risks involved with MRE

The MRI machine creates a strong magnetic field around you, and radio waves are directed at your body. The procedure is painless. You don't feel the magnetic field or radio waves, and there are no moving parts around you. During the MRI scan, the internal part of the magnet produces repetitive tapping, thumping and other noises. You might be given earplugs or have music playing to help block the noise.

Because MRI uses powerful magnets, the presence of metal in your body can be a safety hazard if attracted to the magnet. This includes devices such as Metallic joint prostheses, Artificial heart valves, Implantable heart defibrillator, Implanted drug infusion pumps, Implanted nerve stimulators, pacemaker, Metal clips, Metal pins, screws, plates, stents or surgical staples, Cochlear implants, bullet, shrapnel or any other type of metal fragment, Intrauterine device etc.

4. What are the alternatives to treatment?

There are no approved medications for treatment of NAFLD or NASH. Lifestyle modifications based on increased physical activity and healthy diet is the mainstay of treatment. Treatment of comorbidities include medications for diabetes, hypertension, dyslipidaemia as per standard guidelines.

5. What are the possible advantages of participation in this study?

You will be asked to follow lifestyle modifications and diet modifications depending on your group. You will be contacted by a diet coach who will advise you on this. You will also be followed monthly in the beginning for 6 months followed by every 3 months till the end of the study. During the follow up you will be asked questions about your well-being, medications, any adverse effects along with investigations.

Since the intervention is in the form of lifestyle modifications and dietary interventions, we do not foresee any serious adverse events. Occasionally there can be a drop in blood sugar levels in diabetic patients due to improvement in glycaemic control. However, you will be continuously monitored for any change in blood sugar level and drug dose will be titrated accordingly. If you are diagnosed with NASH liver biopsy will be performed annually. This can cause pain and bruising at the site of biopsy, bleeding from biopsy site, infection and rarely injury to the nearby structure.

You can decide whether you should participate in the research or not, your participation is completely voluntary. Your regular care in the hospital will not be affected by your decision. If you decide not to join, you need not do anything. You don't have to sign the informed consent form. You are free to withdraw your consent at any time without giving any reason.

6. What happens with your data?

The information collected from you will be kept confidential. Your participation will always remain secret. The data will be stored with a code or a Subject ID. This means that the study documents will have your subject ID instead of your name which represents your information.

7. Are there any costs for participating in the study?

There will be no cost to you for participation in this study. You will not have to pay for any of the medical examinations, procedures or laboratory tests that are required for this study.

8.Visit allowance:

A maximum of 500/- Rs will be given to the participants.

9.AE and SAE:
Following dietary interventions during the first 15 days there can be fatigue and headache which will subside with adequate hydration. Any SAE related to intervention will be reimbursed as per actual on producing bills.

10. Has the ethical reviewing committee approved this research?
The study was reviewed and approved by the Institutional Ethics Committee.

Thank you for reading this information sheet and taking the time to consider participating in this study. If you agree to take part, you will be asked to personally sign and date the Informed Consent Form at the end of this document. A copy of this document will be given to you for your reference and personal records.

The contact details of the Investigator are:

Name of the study investigator	
Phone no.	
Address of study site:	Twins Digital Services India Private Limited 2nd Floor, 418 & 420, 4th Cross Road, HRBR Layout 2nd Block, Kalyan Nagar, Bengaluru 560043, India

If you feel that your rights as a person are violated, you can contact the study doctor and ethics committee:

Ethics Committee Chairman	
Contact Number:	
Address	Medisys Clinisearch Ethical Review Board, Bangalore Diabetes Centre, No 426, 4th cross, 2nd block Kalyanagar, Bangalore 560048

INFORMED CONSENT FORM

Study title: `Efficacy of Twin Precision treatment in patients with Non-alcoholic fatty liver disease (NAFLD and NASH) - a multicenter, open label, parallel arm, randomized controlled trial

Principal Investigator:

Subject's Name:

Date of Birth / Age: **Gender:**

Address of the Subject:

Contact Number:

Qualification: **Occupation:**

Annual Income of the Subject:

Name of the Nominee(s)and his relation to the Subject:

Address of Nominee(s):

Contact No:

Please read and place your initials in each box

1.	I confirm that I have read and understood the information sheet, **Ver_____** I confirm that the study has been explained to me and I have had ample time an opportunity to ask questions.	
2.	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I understand the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	

4.	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	
5.	I hereby acknowledged that i have read and understood the company privacy policy and consent to provide my stool sample for GUTMICROBIOME test. I also consent to use my data for research and academic purposes.	
6.	I agree to take part in the above study and to follow all study procedures as detailed above	

I agree to take part in the above study.

_____ _____ _____

Name of Participant Date Signature

If participant is not able to read or write

Signature of impartial witness

_____ _____ _____

Impartial Witness Date Signature

_____ _____ _____

Name of Legally Relation Signature

accepted representative (if applicable)

_____ _____

Contact No: Date

Signature of the person conducting the Informed Consent:

I confirm that I have fully explained all aspects of the trial to the subject (or legally acceptable representative.

_____	_____	_____
Name of Principal Investigator	Date	Signature.