A Randomized Trial to Improve Quality of Life in People with Cirrhosis – the Mi-Kristal RCT

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A Randomized Trial to Improve Quality of Life in People with Cirrhosis – the Mi-Kristal RCT

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SUMMARY

Study Name	A Randomized Trial to Improve Quality of Life in People with Cirrhosis – the Mi-Kristal RCT
Subject Population	At least 50 patients with cirrhosis and portal hypertension, with no previous lactulose use, and moderate to high self-reported daily activity impairment.
Objective	To determine if lactulose therapy improves health-related quality of life (HRQOL), cognitive function, sleep quality and activity level impairment and reduces number of falls.
Design	Randomized two-arm study of lactulose
Arms	Treatment: Crystalized Lactulose (Kristalose) Control: No intervention
Procedures	- Screen cirrhosis patients and determine if they meet inclusion and exclusion criteria. - Determine regular daily activity level impairment using WPAI; consent and randomize patients. - Collect demographic information and conduct baseline assessments: questionnaires assessing HRQOL, cognitive function, sleep quality, health history and current alcohol use. - Randomized subjects receive 28 days of crystallized lactulose therapy (20g twice daily (b.i.d.)) or no therapy. - Automated SMS or email follow-up at 3, 6, 9, 14, 15, 21 and 28 days with patients in treatment group: assess bowel movements; may be done via email or phone if required. - 28-day follow-up evaluation consists of questionnaires assessing HRQOL, cognitive function, sleep quality, falls and activity level impairment.
Site	Michigan Medicine, Ann Arbor, MI

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SIGNIFICANCE

Cirrhosis is the final common pathway for all chronic liver diseases.(1) It is common, with a US prevalence >1 million and rising owing to age-related metabolic comorbidities.(2) Two-thirds of contemporary patients with cirrhosis are now ≥ 60 years old.(3) The mortality and healthcare costs associated with cirrhosis have nearly doubled within the last 10 years.(4, 5) More than any other factor, these adverse outcomes are driven by the development of hepatic encephalopathy (HE). A spectrum of reversible cognitive changes, HE ranges from inattention and executive function deficits with poor quality of life (QOL) to a severe form marked by lethargy, disorientation, and even coma.(3-6) Over 40% of patients with cirrhosis will develop HE.(6, 7) HE is associated with increased mortality, malnutrition, sarcopenia,(8) frailty,(9) debility,(10) falls,(11-13) and frequent hospitalization.(14)

HE is caused by brain exposure to ammonia, a waste product of bacterial metabolism in the gut. Normally the liver converts ammonia to urea. Unfortunately, owing to technical challenges in its measurement and confounding factors in the pathogenesis of HE, the level of ammonia in the blood is a poor biomarker for the risk or presence of HE. Leveraging the concept that HE presents as a spectrum with early, subclinical stages presenting with poor quality of life (QOL), we have used the presence of poor QOL to predict the development of HE.(15) We have found that answers to a one-question 0-10 scale rating the impact of cirrhosis on one's daily activity efficiently distinguishes patients with low 1-year risk of HE from those with high risk.(15) In clinical practice many clinicians detect disturbances in QOL or functioning that could be associated with HE and empirically start HE-directed therapy. In this trial we will extend our prior research by enrolling patients at high risk of overt HE and formally test the benefits of QOL-triggered HE therapy.

1. STUDY OBJECTIVES

The primary objective is to determine whether lactulose therapy in a study population of cirrhosis patients with portal hypertension improves their health-related quality of life (HRQOL). We will be using crystalized lactulose (Kristalose, Cumberland Pharmaceuticals). We have 6 specific aims, which are detailed below

1.1 SPECIFIC AIMS

1.1.1 Primary Aim

Aim 1: To determine whether lactulose therapy improves self-reported HRQOL as assessed using the Short Form-8 Health Survey (SF-8).

1a. Comparison of SF-8 scores from baseline to 28 days, between the intervention and control arm.

1.1.2 Secondary Aim

Secondary aim of this trial include:

Aim 2: To determine whether lactulose therapy improves cognitive function as assessed using the Animal Naming Test (ANT).

2a. Comparison of ANT scores from baseline to 28 days, between the intervention and control arm.

1.1.3 Exploratory Aims

Aim 3: To determine whether lactulose therapy improves overall sleep quality as assessed using the Pittsburgh Sleep Quality Index (PSQI).
3a. Comparison of PSQI overall sleep quality ratings from baseline to 28 days, between the intervention and control arm.

Aim 4: To determine whether lactulose therapy improves regular daily activity impairment as assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI).
4a. Comparison of self-reported regular daily activity impairment scores as part of WPAI from baseline to 28 days, between the intervention and control arm.

1.1.3 Exploratory Adverse Event Aims

Aim 5: To determine if lactulose therapy increases the incidence of >5 self-reported bowel movements per day.
5a. Comparison of self-reported episodes of >5 daily bowel movements from baseline to 28 days between the intervention and control arm.

Aim 6: To determine if lactulose therapy reduces the number of self-reported falls.
6a. Comparison of self-reported number of falls from baseline to 28 days between the treatment and control arm.

1.2 END POINTS

All patients will be followed until death, liver transplantation or final study visit at 28 days post – enrollment.

Primary Endpoint

1. Comparison of SF-8 at 28 days post-baseline, between the two groups.

Secondary Endpoints

1. Comparison of ANT, overall sleep quality, regular daily activity impairment, falls, and average number of daily bowel movements at 28 days, compared between the two groups.

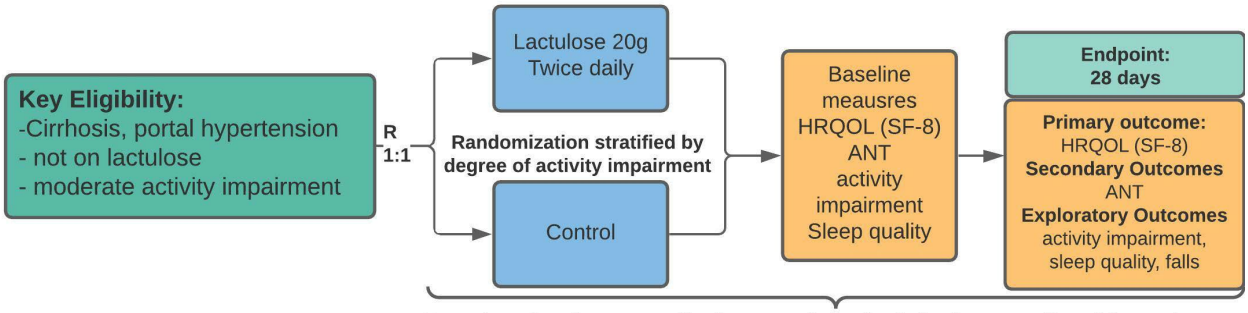
2. STUDY DESIGN

Overview: We propose a randomized two-arm parallel group trial to determine if lactulose therapy in cirrhosis patients with portal hypertension who report moderate to high regular daily activity impairment and have no history of prior lactulose use or HE within 6 months, improves their HRQOL, cognitive function and overall sleep quality at 28 days post-baseline. Subjects will be randomized to one of two groups:

1) Treatment: subjects prescribed and instructed to take 20g (dissolved in 4oz of water) dose of lactulose twice daily (upon awakening and then 4 hours later) for 28 days.
2) Control: subjects are asked to complete baseline and outcome assessments at 28 days and no intervention or placebo will be prescribed.

Our goal is to have 50 patients with cirrhosis who meet study eligibility criteria (see Section 3 below) complete study participation, with approximately 25 subjects in each arm. We will enroll up to 75 subjects to account for subject withdrawals, lost to follow-up, death, transplant or PI discretion.

Figure 1. Study Design



We will enroll patients with cirrhosis who report impairment of daily activities, defined by scores ≥3 on the 0-10 activity impairment scale from the Work-Productivity Activity index and assess the impact of lactulose therapy on health-related qualoty of life (HRQOL), cognitive function (animal naming test, ANT), sleep quality, and falls

3. SELECTION AND ENROLLMENT OF SUBJECTS

3.1 INCLUSION CRITERIA

All subjects must meet the following criteria:

1. *Adult ≥ 18 years of age*
2. *Diagnosis of cirrhosis – must meet one of the following criteria:*
   - a. *liver biopsy, OR*
   - b. *history of cirrhosis complication: ascites, variceal bleeding, hepatic encephalopathy, OR*
   - c. *2 of the following 4 criteria:*
     1. *US, CT or MRI imaging findings of cirrhosis (cirrhotic appearing liver, splenomegaly, varices, ascites)*
     2. *Fibroscan liver stiffness score >13 kPa*
     3. *Laboratory testing: AST/platelet ratio index (APRI) >2.0*
     4. *CT, MRI or EGD showing presence of esophageal varices*
3. *Evidence of portal hypertension – must meet at least one of the following criteria:*
   - a. *Ascites*
   - b. *Varices (seen by endoscopy or by ultrasound or cross-sectional imaging)*
   - c. *Fibroscan liver stiffness measurement (LSM) > 25*
   - d. *Platelets < 80*
4. *Moderate activity impairment*
   - a. *≥ 3 on WPAI regular daily activity impairment question (scored 0-10)*

3.2 EXCLUSION CRITERIA

The following exclusion criteria applies to all subjects:

1. *Non-English speaking*
2. *Unable or unwilling to provide consent*

3. *History of liver transplant*
4. *Disorientation at the time of enrollment, Dementia, or Treated Memory Disorder*
5. *History of prior lactulose use or HE within 6 months*
6. *Metastatic solid malignancy or blood malignancy*
7. *A1C > 12 (within past year)*
8. *Low galactose diet*

3.3 STUDY ENROLLMENT PROCEDURES

3.3.1 Identification and recruitment

After IRB approval, patients will be identified and recruited from multiple centers including Michigan Medicine. Patients will be identified by one of 6 methods: 1) referral by Michigan Medicine Hepatology providers, 2) screening of Michigan Medicine clinic schedules on the outpatient, transplant or procedure liver services, 3) referral from study coordinators of pre-existing registry studies at Michigan Medicine, 4) screening electronic medical records of Michigan Medicine hospitalized patients, 5) posting of study on www.UofMHealthResearch.org, 6) direct emails sent to cirrhosis patients via REDCap.

Patients with cirrhosis who have an email address are eligible to be contacted for recruitment by email via REDCap (see Appendix G). This will be conducted via a supplementary REDCap database in addition to the Mi-Kristal REDCap database. The supplementary REDCap database will be set to send a marketing email to new cirrhosis patients as they are added. The email will be shown as being sent from a group email: mikristalstudy@med.umich.edu. Anyone interested can fill out an interest form via supplementary REDCap database and provide their contact information to the study team on this form. Once we receive the contact information, we will proceed to contact the patient via phone and proceed with enrollment and consent if they are interested. The study team will subsequently reach out to the patient by phone or email to complete the screening and enrollment process. Eligible patients at Michigan Medicine will be contacted by phone, email, or in-person to see if they are interested in participating in the study. To verify patient eligibility prior to enrollment, study staff will ask patients final screening questions as outlined in (see Appendix F).

3.3.2 Monitoring of recruitment targets

Data will be collected on all patients who are screened. A screening log will be maintained and will include the inclusion/exclusion criteria in Sections 3.1 and 3.2 above, and hence confirm eligibility or provide the reasons for ineligibility, as well as reasons for nonparticipation of eligible subjects. This will include: 1) the number of all persons screened with cirrhosis, 2) reasons for exclusion (specific criteria), 3) the number approached for participation, 4) the number enrolled, 6) the number who declined participation and 7) reasons for nonparticipation.

3.3.3 Consent Procedures

We will obtain written informed consent for participation from at least 50 subjects. A study coordinator will obtain informed consent. If recruitment procedures are being conducted in person, patients will be approached at the time of scheduled clinic appointments, procedures, or during hospitalizations. The study coordinator will obtain written informed consent during the in-person interaction. A copy of the informed consent form (ICF) will be provided to the subject.

If recruitment procedures are being conducted via email or phone, they will be consented electronically via SignNow, a third-party service to digitally collect informed consent which meets the requirements for HIPAA-compliance in the US. A copy of the informed consent form will be made available to the patient via email, or they can download a copy through SignNow.

4. STUDY INTERVENTIONS AND PROCEDURES

4.1 ASSESSMENTS

4.1.1 Baseline Assessments

1. Demographics Questionnaire (DQ) (Appendix A)
Participants will be asked to provide the following demographic information:
1. Sex
2. Age
3. Ethnicity
4. Race
5. Highest education level attained
6. Marital status
7. Occupation status
8. Income
9. Rural/Urban residence

2. Health History Questionnaire (HHQ) (Appendix B)
Participants will be asked to provide the following information:
1. Cause of cirrhosis
2. History of liver cancer
3. Liver transplant waitlist status
4. Driving status
5. Disability status (Katz-ADL)
6. Hospitalization within past 90 days
7. Emergency Room visit within past 90 days
8. Ascites status
9. Currently taking diuretics
10. Paracentesis within past 90 days
11. Hepatic encephalopathy status
12. Medications taken for HE
13. Dialysis status
14. Diabetes status
15. Congestive heart failure status
16. Chronic obstructive pulmonary disease status
17. Overall sleep quality *(PSQI)*
18. Falls in past 4 weeks
19. Average number of bowel movements per day

3. Short Form-8 Health Survey (SF-8) (Appendix C)
The SF-8 is an abbreviated version of an original 36-item health survey (SF-36). It is a generic multipurpose quality of life instrument. It contains psychometrically based physical and mental

health summary measures. The eight domains include general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health and role emotional.

4. Animal Naming Test (ANT) (Appendix D)
   The animal naming test is a timed test that consists of subjects listing as many unique animals as possible in 60 seconds. This is a validated test used for the assessment of hepatic encephalopathy.

5. Alcohol Use Disorders Identification Test-C (AUDIT-C) (Appendix E)
   The AUDIT-C is a brief 3-item alcohol screening instrument that reliably identifies persons who are hazardous drinkers or have active alcohol use disorders.

4.1.2 28-Day Follow-Up Assessments

1. Health Follow-Up Questionnaire (HFUQ) (Appendix G)
   Participants will be asked to provide the following information:
   1. Hospitalizations during study period
   2. Overall sleep quality *(PSQI)*
   3. Falls during study period
   4. Average number of bowel movements per day
   5. Ability to do regular daily activities *(WPAI)*

2. Short Form-8 Health Survey (SF-8) (Appendix C)
3. Animal Naming Test (ANT) (Appendix D)

4.2 ENROLLMENT PROCEDURES

4.2.1 Enrollment

After informed consent procedures, all subjects will complete enrollment procedures in the following order:

a. Provide their contact information
b. Randomization
c. Baseline assessments
d. Kristalose allocation and intervention counseling *(only if randomized to treatment group)*

In the control group, the date subjects are randomized and complete the baseline assessments is Study Day 1. These procedures can be conducted in person or via phone. In the treatment group, the date subjects receive Kristalose and receive intervention counseling is Study Day 1.

4.2.2 Randomization

After informed consent and baseline procedures are completed, the study coordinator will randomize the subject via reandomize.net. Subjects will be randomized in approximately equal allocation to each arm 1:1 lactulose therapy or the control group. Randomization is stratified by subject self-reported activity impairment level. Activity impairment level is determined by the baseline WPAI regular daily activity impairment score collected as part of the final screening questions (Appendix F): mild/moderate is a score of ≤7, severe is a score of >7. To ensure approximate balance within arms, the randomization will be implemented using a randomly permuted blocks design to ensure approximate balanced assignments within subject self-reported

activity impairment severity level. The sequence of assignments for each stratum will be prepared in advance by a biostatistician.

4.2.3 Baseline Assessments

The study coordinator will conduct the following assessments with all subjects via phone, REDCap survey email or in person, after consent and randomization processes are complete:

1. Demographics Questionnaire
2. Health History Questionnaire
3. SF-8
4. ANT
5. AUDIT-C

4.3 INTERVENTION PROCEDURES

4.3.1 Lactulose Administration and Duration

Subjects randomized to the control are not required to complete any intervention activities or treatments. For subjects randomized to lactulose therapy, the following steps to implement the intervention will occur on Study Day 1:

1. The Principal Investigator (PI) will prescribe lactulose to subjects enrolled at Michigan Medicine. Lactulose (Kristalose) will be allocated to the patient in person at the University of Michigan through the Investigational Pharmacy. If enrollment procedures were conducted remotely, the patient will be allowed up to two weeks to schedule an appointment with the study coordinator to receive Kristalose.

2. Subjects will be instructed to take 20g of Kristalose (1 packet) in 4oz water twice daily for 28 days. All patients randomized to lactulose will receive standard counselling.

3. First, all subjects will be instructed to take the first dose on awakening and the second dose approximately 4 hours after the first dose.

4. Second, subjects will be asked to monitor their bowel movements (see section 4.3.2 Adherence Assessment below). If they achieve ≥ 4 bowel movements in one day outside of the adherence assessments, they will be asked to contact the study team directly and will be instructed to reduce their lactulose frequency to one 20g dose daily. No dose adjustments will be made to *increase* bowel movements. Study staff will be alerted via email if a subject reports more than 4 bowel movements per day. Subjects will be instructed to call the study phone line if their bowel movements do not decrease with a reduced dose. They will also be instructed to notify the study team if they are undergoing proctoscopy or colonoscopy and to avoid taking nonabsorbable antacids (like aluminum or magnesium hydroxide) with Kristalose since these may interfere with the lactulose activity.

5. Third, patients will be counselled on the side effects of lactulose including mild bloating, cramping or diarrhea. If the symptoms worry the patient, they will be instructed to reduce lactulose to one 10g dose on awakening and then to increase to 10g twice daily as tolerated.

4.3.2 Adherence Assessment

During the 28-day intervention phase, all subjects will be contacted on Study Days 3, 6, 9, 14, 15, 21 and 28 via automated REDCap email or SMS text messages via Twilio service. Study Day 28 will only be collected via REDCap email or phone. These points of contact are to collect data about stool frequency and consistency among all subjects and therefore lactulose adherence in the treatment group. If the subject opts out of Twilio service, the subject can also receive these questions via REDCap automated email or a study coordinator will collect this data from the subject directly via phone or email. On Study Days 3, 6, 9, 14, 21 and 28 subjects will be asked the following questions:

1. "How many bowel movements did you have yesterday? Please respond with a whole number." *If 0-4 bowel movements are reported the subject will exit the survey. If >4, the subject will receive the following instructions:*

> Since you had > 4 bowel movements yesterday, please reduce to **one** 20g dose of kristalose (1 packet) packet per day. Please call the study line at 734-232-4182 if you continue to have more than 4 bowel movements daily or with any questions or concerns.

On Study Day 15 subjects will be asked:

2. "Please reference the Bristol Stool Chart we provided to you to answer this question. How would you describe your stool looks today? Please respond with the applicable number, between 1-7. *All subjects exit survey after response.*

1. Separate hard lumps
2. Sausage-shaped but lumpy
3. Like a sausage but with cracks on its surface
4. Like a sausage or snake, smooth and soft
5. Soft blobs with clear cut edges
6. Fluffy pieces with ragged edges, a mushy stool
7. Watery, no solid pieces, entirely liquid

4.3.3 Handling of Study Drug

Kristalose is an FDA approved drug. We established an agreement with the manufacturer Cumberland to provide Kristalose supply. Kristalose will be distributed through Cumberland to the investigational drug pharmacy at Michigan Medicine. The study team will liaise with the investigational pharmacy and manufacturer to ensure that an adequate supply of drug is available for dispensing.

The investigational pharmacy is responsible for receipt, storage, dispensing, and reconciliation of the study drug. Pharmacy accountability will be monitored. The investigational pharmacy will maintain accountability logs for all supplies of Kristalose. These logs will include the purchase date (date received), lot number, expiration date, and quantity of all Kristalose supplied for the trial. In addition, every dose dispensed will also be recorded in a subject-specific accountability log. The Kristalose lot number for each dose dispensed will be recorded and the inventory balance will also be noted on the accountability log. Study drug shipping receipts will be retained. The investigational pharmacy will dispense 2 packages (30 20g dose packets in each package) of Kristalose to each subject randomized to the treatment group upon receipt of randomization notification either in person at Michigan Medicine or shipped directly to the patient via FedEx.

4.4 FOLLOW-UP AND OUTCOMES

The final follow-up study visit will occur 28 days post-baseline (SD 28±5). Primary and secondary outcome data will be collected at this visit. The SF-8, ANT and Health Follow-Up Questionnaire (see Appendix H) will be conducted with all subjects. The Health Follow-Up Questionnaire contains several questions from the baseline Health History Questionnaire including hospitalization data, overall sleep quality (PSQI), number of falls, number of bowel movements per day and regular daily activity impairment score (WPAI). This visit will be conducted via REDCap email and/or phone.

Table 1. Procedure Table

		STUDY DAY						
	Entry/ Day 1*	3	6	9	14	15	21	28 (SD 28 ± 5 days)
Informed Consent	X							
Randomization	X							
Contact Information	X							
Demographics Questionnaire	X							
Health History Questionnaire	X							
Short Form Health Survey 8	X							X
Animal Naming Test	X							X
AUDIT-C	X							
Health Follow-Up Questionnaire								X
Twilio/REDCap Email Automated Messages		X	X	X	X	X	X	X
Lactulose Therapy	X	X			→			X

** Control Group: Study Day 1 is defined as the calendar day on which the subject is randomized. Treatment Group: Study Day 1 is defined as the calendar day on which the subject receives Kristalose.*

4.5 DISTINCT CLINICAL SCENARIO: PATIENT DEATH

In the event of a subject's death during the study period we will attempt to ascertain the date and cause of death, and hospitalization data that is available in the subject's Michigan Medicine electronic medical record.

4.6 DISTINCT CLINICAL SCENARIO: PATIENT HOSPITALIZATION

In the event of a subject's hospitalization during the study period, we will record the event as an Adverse Event (AE). If the subject's hospitalization coincides with study activities, we will revise each procedure as follows:

1) Lactulose therapy: If a subject in the treatment group is hospitalized at Michigan Medicine during the study, the study PI and/or coordinator will contact the Michigan Medicine care team to discuss continuation of lactulose therapy during the hospitalization. If the hospitalization is a result of an AE from lactulose use, this will be discussed with the PI and lactulose may be paused or discontinued.
2) Follow-up phone study visits: If the hospitalization coincides with the Day 28 follow-up visit, we will provide the subject an opportunity to reschedule the visit after discharge, under PI discretion.

4.7 DISTINCT CLINICAL SCENARIO: OVERT HE DIAGNOSIS & INITIATION OF LACTULSOE THERAPY

If a subject in either group (treatment or control) is diagnosed with Overt HE, or prescribed lactulose for any clinical reason outside of study participation during the study period, their participation in the study will be terminated. An early termination visit will be conducted with the subject to collect outcome data including the SF-8, ANT and Follow-Up Health Questionnaire.

4.8 EARLY TERMINATION VISIT

If a subject discontinues participation in the study, the subject will be asked to complete all 28 Day Follow Up Assessments at the time of discontinuation including the SF-8, ANT and Follow-Up Health Questionnaire. If they choose not to complete them, their participation will be terminated immediately. All data collection prior to termination will be retained by the study team.

4.9 SUBJECT INCENTIVES

Participants will be offered a $50 compensation for completing all activities in the trial.

5. MANAGEMENT OF ADVERSE EVENTS AND PROTOCOL DEVIATIONS

5.1 PROTOCOL DEVIATIONS

Minor protocol deviations that do not impact the safety of participants or the integrity of data must be recorded and reported to the Institutional Review Board (IRB) on an annual basis as part of standard continuing review. Major protocol deviations that may impact participant safety or the integrity of data are required to be reported to the IRB as an ORIO within 7 days of knowledge of the event.

5.1.2 Protocol Deviations may include the following items, among others:

- Enrollment despite meeting exclusion criteria
- Enrollment despite not meeting inclusion criteria
- Consent not obtained in accordance with IRB guidelines
- Baseline assessments not collected
- Outcome assessments collected outside of prescribed study window
- Outcome assessments not collected

5.2 ADVERSE AND SERIOUS ADVERSE EVENT DEFINITIONS & REPORTING

5.2.1 Adverse and Serious Adverse Event Definitions (AE & SAE)

In the Mi-Kristal study an AE is defined as any untoward or unfavorable physical, social or psychological occurrence in a participant that can be temporally associated with the subject's participation in the study, whether or not considered directly related to the subject's participation in the research. An AE is considered an SAE if the event results in death or permanent disability and is definitely related to the subject's participation in the study. However, due to the nature of the participants enrolled and low risk nature of the treatments, the AEs and SAEs recorded and reported to the IRB will be limited using the following guidance.

All hospitalizations will be reported as AEs. Other events that are not attributable to their participation in the study will not be reported as AEs, even if the data are collected for study purposes (e.g. car accident, stroke, myocardial infarction etc.). The exception to this standard is death, which will always be reported as either an AE or SAE. Additionally, expected clinical issues that subjects experience related to their ongoing medical care or chronic health problems will not be considered AEs unless it involves any of the above mentioned AE examples. Any AEs that are attributable to the study will be reported and adhere to the AE Reporting Timeline (see Table 3 below). The 28±7 days end point is our final contact with subjects in which we will collect AE and SAE information. Events which qualify as AEs will be classified using the following IRB standards:

5.2.2 AE Relatedness and Severity

For all AEs, the PI (Dr. Elliot Tapper) will use his best judgment and indicate how related the AE is to the research procedures and intervention. He will assign the AE to one of the four categories below:

- **Definitely related:** The AE ***is clearly related*** to the intervention
- **Probably related:** The AE **is likely related** to the intervention
- **Possibly related:** The AE **may be related** to the intervention
- **Unlikely to be related:** The AE **is doubtfully related** to the intervention
- **Definitely not related:** The AE **is definitely not related** to the intervention

The PI will provide an AE severity*:*

- **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- **Moderate:** minimal, local, or noninvasive intervention indicated
- **Severe:** Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
- **Life-threatening:** Life-threatening consequences; urgent intervention indicated
- **Fatal**

The PI will AE level of expectedness:

- **Unexpected adverse events:** (i.e., has NOT been addressed or described in one or more of the following: informed consent document for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation)

- **Expected adverse events:** (i.e., has been addressed or described in one or more of the following: informed consent document for this study, IRB application for this study, grant application or study agreement, protocol or procedures for this study, investigators' brochure or equivalent (for FDA regulated drugs or devices), DSMB/DSC Reports, published literature, other documentation, or characteristics of the study population.

5.2.3 IRBMED Reporting

AEs, SAEs, UaPs and protocol deviations will be reported to IRBMED following IRBMED reporting guidelines.

5.3 CRITERIA OF INTERVENTION DISCONTINUATION

If the subject experiences any SAE that might be considered related to Mi-Kristal participation, the study coordinator will inform the subject to stop all intervention activities. The PI will decide whether to continue study activities thereafter. Every effort will be made to maintain the subject's participation in follow-up activities. If lactulose therapy is terminated before 28 days, the Day 28 outcome assessments will be collected within 5 days of lactulose termination.

6. STATISTICAL CONSIDERATIONS

6.1 SAMPLE SIZE AND ACCRUAL

While no studies of lactulose enrolling patients exclusively with deficits in quality of life, one high quality study of lactulose therapy have been performed for patients with cognitive dysfunction defined by psychometric testing. Lactulose was associated with a 6.81 95%CI (5.2-8.4) point or 65% relative improvement in health-related quality of life using the Sickness Impact Profile compared to control. Given this magnitude of effect, very few patients need to be enrolled. However, if we hypothesize an attenuated effect (30% improvement), seeking to enroll with a 1:1 randomization, assuming an alpha of 0.05, we will have 90% power to detect a difference among 42 subjects. We will therefore proceed with a study of 50 patients to allow for additional adjustment of baseline covariates and drop-outs.

6.2 QUANTITATIVE ANALYSIS

We will compare differences in all outcomes, each continuous variable, using MANOVA. Multiple linear regression will be used to adjust for baseline covariates.

7. DATA COLLECTION AND MANAGEMENT

7.1 RECORDS TO BE KEPT

All data will be entered into case report forms (CRFs) using a REDCap platform. These forms include enrollment, baseline, intervention and outcome assessments. All data recorded in REDCap is identified by a unique Study Identification Number (Subject ID). The subject must read, understand, and sign an IRB approved informed consent form (ICF). The Investigator will retain the original signed consent form in a secured location. Additionally, we will upload a copy of original signed ICF into the subject's Michigan Medicine electronic medical record. Separate documents will be de-identified and stored in the University Share Drive.

7.2 ROLE OF DATA MANAGEMENT

The primary study coordinator will be responsible for data management. The study portal will provide a highly structured repository to store and process study data from electronic case report forms (e-CRFs), as well as to protect its integrity and confidentiality. This tool will assist study staff by providing efficient protocol management and study retention and oversight. Access to the study portal will be granted by the Investigator or primary study coordinator with differential access rights based on role.

7.2.1 Data Collection Protocol

- For enrollment, study staff will access the REDCap study portal via the web, and provide screening information about the patient.
- Study-related data, as outlined in the intervention procedures above, will be entered online by research staff into the CRFs within the REDCap study portal.

7.3 DATA SECURITY AND CONFIDENTIALITY

We will keep a separate password protected screening log and subject tracker on the University shared drive in a secured location. Only study personnel will have access to the electronic screening log that maps the Subject ID number and Screening ID number (if applicable) to the subject's name, medical record number (MRN) and contact information. Only limited identifiable data will be collected. All subject data recorded on paper are maintained in locked file cabinet with limited access by research staff. No one other than the research team at the University of Michigan will be given or have access to the patient's name, mailing address, email address, phone number, and other personal identifying information.

7.4 USE OF TWILIO SERVICE

We will work with the Michigan Institute for Clinical and Health Research (MICHR) to construct our REDCap database and connect it with Twilio. Twilio (https://www.twilio.com) is a third-party service used to send automated SMS messages and phone call surveys to users for a variety of purposes. We will use Twilio to send follow-up communications to subjects in the intervention groups on Study Days 3 3, 9, 9, 14, 21 and 28. The only piece of information transmitted from our REDCap database to Twilio will be the phone number of the participant. Participants will choose to either opt-in or opt-out of using Twilio service. Participants that choose to opt-in to the service must provide informed consent to use the service and must agree to Twilio's privacy policy and terms of service. All participants who refuse to use the Twilio service will be offered alternative means of follow-up including phone, text, and/or email communications directly sent from the study coordinator. No protected health information (PHI) will be requested from the patients or sent by the study team through Twilio. The only information transmitted through Twilio SMS text messages or phone calls will be non-identifiable responses to questions about the number of times per day the subject has bowel movements.

8. HUMAN SUBJECTS

8.1 INSTITUTIONAL REVIEW BOARD AND INFORMED CONSENT

This protocol, the informed consent document, and any subsequent modifications will be reviewed and approved by the Michigan Medicine IRB (IRBMED). The consent form will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. A copy of the consent form will be given to the participant, a copy uploaded to MiChart (if the subject is a Michigan Medicine patient), and the original signed consent will be stored by the coordinator in a secure location.

8.2 SUBJECT CONFIDENTIALITY

All subject evaluation forms and other records will be identified only by the Subject ID and date of completion, to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry will be performed using Subject ID only. Any clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB.

8.3 POTENTIAL RISKS AND BENEFITS

There is minimal medical risk to any participant in this study. Patients will be counselled on the risk of cirrhosis complications (ascites, HE) that may be related to their underlying disease as well as side effects associated with lactulose: abdominal discomfort, bloating, diarrhea, dehydration and rarely hypernatremia and/or hypokalemia. Participants can withdrawal at any time. The potential benefits to participants include an improvement in HRQOL, cognitive function and overall sleep quality and reduction in the risk of developing HE.

The known or expected risks are:

- **Questionnaires:** Many of the questions relate to how the subjects are feeling, and this may lead to an emotional reaction. To minimize these risks, questions will not ask explicitly sensitive information and study coordinators will be available for support. Additionally, should the questionnaires or surveys become uncomfortable, subjects can choose to skip any question that they do not wish to answer or stop at any time.
- **Loss of confidentiality:** There is rare risk of loss of confidentiality or privacy. To reduce the risk of loss of confidentiality, trained members of the research team will ask subjects questions in a private patient room. This information will be limited to the subject's name, date of birth, sex, and subject ID. Information such as the subject's full name and phone number will be recorded along with their baseline data however, this information will be stored in a locked cabinet. This data will be entered into a password-protected database where all data will be coded using a study number and only staff involved in this research will have access to the data.
- **Lactulose**: There is the possibility that that lactulose can cause physical symptoms such as abdominal pain, diarrhea, and bloating. Lactulose can rarely cause dehydration and hypernatremia (low blood sodium) and/or hypokalemia (low blood potassium).

There may be additional risks that are unknown or unexpected.

8.4 STUDY MODIFICATION/DISCONTINUATION

The study may be modified or discontinued at any time by Michigan Medicine IRB as part of their duties to ensure that research subjects are protected. Any changes to the protocol or consent form require a written protocol amendment that must be approved by the IRB prior to implementation. These amendments, should they be required, will become part of the protocol and maintained by the Investigator as part of study documentation. If the Investigator or study coordinator implements a protocol change prior to IRB approval, the coordinator must notify the IRB via an ORIO report.

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APPENDICES

Appendix A. Demographics Questionnaire
Appendix B. Health History Questionnaire
Appendix C. Short Form Health Survey-8 (SF-8)
Appendix D. Animal Naming Test (ANT)
Appendix E. Alcohol Use Disorder Identification Test (AUDIT-C)
Appendix F. Final Screening Questions
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Appendix A. Demographics Questionnaire

Mi-Kristal Trial Demographics Questionnaire

Instructions: Please answer the following demographics questions. Please note that your answers will be kept completely confidential. Please record the date the form was completed on the top of this page.

1. What is your age in years?

   Age: _____

2. What is your sex?

   ☐ Male

   ☐ Female

   ☐ Other (please state): _____

3. What is your ethnicity?

   ☐ Hispanic or Latino

   ☐ Not Hispanic or Latino

   ☐ Unknown

   ☐ Not Reported

4. What is your race? (select all that apply)

   ☐ American Indian or Alaska Native

   ☐ Asian

   ☐ Black or African-American

   ☐ Native Hawaiian or Other Pacific Islander

   ☐ White

   ☐ Unknown

   ☐ Not Reported

5. What is the highest education level that you have completed?

   ☐ No schooling completed

   ☐ Some high school, no diploma

   ☐ GED or equivalent

   ☐ Nursery school to 8th grade

   ☐ High school graduate

   ☐ Some college, no degree

   ☐ Associate degree: occupational, technical, or vocational program

   ☐ Associate degree: academic program

   ☐ Bachelor's degree (e.g., BA, AB, BS, BBA)

   ☐ Master's degree (e.g., MA, MS, MPH, MEng, MEd, MBA)

   ☐ Professional school degree (e.g., MD, DDS, DVM, JD)

   ☐ Doctoral degree (e.g., PhD)

   ☐ Unknown

6. What is your marital/partner status?

   ☐ Never Married/Single

   ☐ Separated

- ☐ Married
- ☐ Divorced
- ☐ Domestic Partnership
- ☐ Widowed

7. What is your current employment status?

- ☐ Employed full-time
- ☐ Employed part-time
- ☐ Retired
- ☐ On disability
- ☐ Not employed

8. What is your annual income?

- ☐ Less than $10,000
- ☐ $10,000 to $14,999
- ☐ $15,000 to $24,999
- ☐ $25,000 to $34, 999
- ☐ $35,000 to $49,999
- ☐ $50,000 to $74,999
- ☐ $75,000 to $99,999
- ☐ $100,000 to $149,999
- ☐ $150,000 to $199,999
- ☐ $200,000 or more
- ☐ Unknown

9. What type of geographic area do you live in?

- ☐ Rural
- ☐ Suburban
- ☐ Urban

Appendix B. Health History Questionnaire

Mi-Kristal Trial Health History Questionnaire

Instructions: Please answer the following questions about your health history to the best of your knowledge. Please record the date the form was completed on the top of this page.

1. What is the underlying cause of your cirrhosis? (check all that apply)
   - ☐ Alcohol
   - ☐ Hepatitis C
   - ☐ Hepatitis B
   - ☐ Autoimmune Hepatitis
   - ☐ Nonalcoholic fatty liver disease (NAFLD)
   - ☐ Primary biliary cirrhosis (PBC)
   - ☐ Primary sclerosing cholangitis (PSC)
   - ☐ Other (please specify): _____
2. Do you currently have liver cancer?
   - ☐ Yes
   - ☐ No
   - ☐ Unknown
   a. If "No" or "Unknown," do you have any history of liver cancer?
      - ☐ Yes
      - ☐ No
      - ☐ Unknown
3. Are you on the liver transplant waiting list?
   - ☐ Yes
   - ☐ No
   - ☐ Currently undergoing transplant evaluation
   - ☐ Recently removed from the transplant waiting list

   4.1 If recently removed, how long ago was removal (in months): _____

   4.2 If recently removed, specify reason for removal: _____
4. Have you stopped driving within the past 6 months?
   - ☐ Yes
   - ☐ Stopped driving more than 6 months ago
   - ☐ No
5. Are you dependent upon assistance from anyone for any of the following (check all that apply)?
   - ☐ Bathing
   - ☐ Dressing
   - ☐ Using the toilet/going to the bathroom
   - ☐ Getting out of bed or chair
   - ☐ Eating
   - ☐ None

6. Have you been hospitalized in the past 90 days?

☐ No

☐ Yes

6.1 If yes, number of hospitalizations: ☐ 1 ☐ 2 ☐ 3 ☐ More than 3

7. Have you had an Emergency Room (ER) visit in the past 90 days?

☐ No

☐ Yes

7.1 If yes, number of ER visits: ☐ 1 ☐ 2 ☐ 3 ☐ More than 3

8. Do you have ascites (accumulation of fluid in the abdomen)?

☐ Yes

☐ No

☐ Unknown

9. Do you currently take diuretics/water pills (e.g. Lasix/Furosemide, Aldactone/Spironolactone)?

☐ Yes

☐ No

☐ Unknown

10. Have you had a paracentesis (a procedure to remove fluid from the abdomen) within the last 90 days?

☐ Yes

☐ No

☐ Unknown

11. Have you have a Transjugular intrahepatic portosystemic shunt (TIPS)?

☐ Yes

☐ No

☐ Unknown

12. Are you currently receiving dialysis?

☐ Yes

☐ No

☐ Unknown

13. Do you have diabetes?

☐ Yes

☐ No

☐ Unknown

14. Do you have congestive heart failure (CHF)?

- ☐ Yes
- ☐ No
- ☐ Unknown

15. Do you have chronic obstructive pulmonary disease (COPD)?

- ☐ Yes
- ☐ No
- ☐ Unknown

16. During the past month, how would you rate your sleep quality overall?

- ☐ Very Good
- ☐ Fairly Good
- ☐ Fairly Bad
- ☐ Very Bad

17. Have you had any falls in the past 4 weeks?

- ☐ Yes
- ☐ No

17.1 If yes, number of falls: _____

18. What is the current (past 2 weeks) average number of bowel movements you have per day?

_____

Appendix C. SF-8

Mi-Kristal Trial SF-8 Health Survey

Instructions: This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. For each of the following questions, please mark an [x] in the one box that best describes your answer**.** Please note that your answers will be kept completely confidential. Please record the date the form was completed on the top of this page.

3. Overall, how would you rate your health during the **past 4 weeks**?

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor ☐ Very poor

4. During the **past 4 weeks**, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?

☐ None at all ☐ Very little ☐ Somewhat ☐ Quite a lot ☐ Could not do physical activities

5. During the **past 4 weeks**, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

☐ None at all ☐ A little bit ☐ Some ☐ Quite a lot ☐ Could not do daily work

6. How much bodily pain have you had during the **past 4 weeks**?

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very Severe

7. During the **past 4 weeks**, how much energy did you have?

☐ Very much ☐ Quite a lot ☐ Some ☐ A little ☐ None

8. During the **past 4 weeks**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

☐ None at all ☐ Very little ☐ Somewhat ☐ Quite a lot ☐ Could not do social activities

9. During the **past 4 weeks**, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

☐ None at all ☐ Slightly ☐ Moderately ☐ Quite a lot ☐ Extremely

10. During the **past 4 weeks**, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

☐ None at all ☐ Very little ☐ Somewhat ☐ Quite a lot ☐ Could not do daily activities

Appendix D. ANT

Mi-Kristal Trial Animal Naming Test

Instructions: Instruct the subject to recall and name as many animals as possible and track the subject's performance for 60-seconds. Set your stopwatch and tell the subject to start when you say GO. Tell the subject to STOP when the stopwatch reads 60-seconds. Keep track of the number of animals they say with the space provided below. When the test is done add your tally marks and indicate the total in the box below. The score is the number of correctly produced animal names during the 60-seconds. Please record the date the form was completed on the top of this page.

Use this space to keep tally of the number of correctly pronounced animal names
SCORE (The sum of all correctly produced animal names)

Appendix E. AUDIT-C

Mi-Kristal Trial AUDIT-C Questionnaire

Instructions: Please answer the following questions related to alcohol use to the best of your knowledge. Please note that your answers will be kept completely confidential. Please record the date the form was completed on the top of this page.

1. How often did you have a drink containing alcohol in the past year?
   - ☐ Never
   - ☐ Monthly or less
   - ☐ 2-4 times per month
   - ☐ 2-3 times per week
   - ☐ 4 or more times a week
2. How many drinks containing alcohol did you have on a typical day when you were drinking in the past year?
   - ☐ 1 or 2 drinks
   - ☐ 3 or 4 drinks
   - ☐ 5 or 6 drinks
   - ☐ 7 to 9 drinks
   - ☐ 10 or more drinks
3. How often did you have six or more drinks on one occasion in the past year?
   - ☐ Never
   - ☐ Less than monthly
   - ☐ Monthly
   - ☐ Weekly
   - ☐ Daily or almost daily

Appendix F. Final Screening Questions

Mi-Kristal Trial Final Screening Questions

Instructions: Below are the final screening questions for potential subjects. Ask potential subjects these questions prior to consent to confirm eligibility. Please record the patient's Screening ID and the date the form was completed on the top of this page. If the patient is enrolled as a subject, this document should be retained in their study chart.

1. Have you ever had a liver transplant? (patient must answer **NO** to be eligible)

   ☐ Yes

   ☐ No

2. Have you ever taken lactulose? (patient must answer **NO** to be eligible)

   ☐ Yes

   ☐ No

3. Have you been told by doctor that you have hepatic encephalopathy (HE) within the past 6 months? (patient must answer **NO** to be eligible)

   ☐ Yes

   ☐ No

4. Are you currently eating a low galactose diet? (patient must answer **NO** to be eligible)

   ☐ Yes

   ☐ No

5. During the past seven days, how much did your CIRRHOSIS affect your ability to do your regular daily activities, other than work at a job? (patient must answer **≥ 3** to be eligible)

   By regular activities we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If CIRRHOSIS affected your daily activities only a little, choose a low number. Choose a high number if CIRRHOSIS affected your activities a great deal.

CIRRHOSIS had no effect on my work — CIRRHOSIS completely prevented me from working

0 1 2 3 4 5 6 7 8 9 10

CIRCLE A NUMBER

6. Based on preliminary screening and these responses, is the patient eligible to participate in this study?

   ☐ Yes, they are eligible, and they have been enrolled. Their subject ID is _____.

   ☐ Yes, they are eligible, but they have not been enrolled because _____.

   ☐ No, they are not eligible because _____.

Appendix G. Health Follow-Up Questionnaire

Mi-Kristal Trial Follow-Up Health Questionnaire

Instructions: Please answer the following questions to the best of your knowledge. Please record the date the form was completed on the top of this page.

1. Have you been hospitalized since you enrolled in this study?

   ☐ No

   ☐ Yes

   6.1 If yes, number of hospitalizations: _____

2. During the past month, how would you rate your sleep quality overall?

   ☐ Very Good

   ☐ Fairly Good

   ☐ Fairly Bad

   ☐ Very Bad

3. Have you had any falls since you enrolled in this study?

   ☐ Yes

   ☐ No

   18.1 If yes, number of falls: _____

4. What is the current average number of bowel movements you have per day? _____

5. During the past seven days, how much did your CIRRHOSIS affect your ability to do your regular daily activities, other than work at a job?

   By regular activities we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If CIRRHOSIS affected your daily activities only a little, choose a low number. Choose a high number if CIRRHOSIS affected your activities a great deal.

CIRRHOSIS had no effect on my work											CIRRHOSIS completely prevented me from working
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

CIRCLE A NUMBER

Appendix H. Bristol Stool Chart

Mi-Kristal Trial Stool Chart

Instructions: This Stool Chart (see below) shows pictures of seven different types of stool. In 15 days, we will contact you and ask you to describe what your stool looks like in reference to this chart.