Cover Sheet

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Patient Buddy App for the Prevention of Avoidable Readmission in Cirrhosis

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Health-IT generated PROs to improve outcomes in Cirrhosis

Sponsor: Agency for Healthcare Research and Quality

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For Peer Review

1. Describe the study hypothesis and/or research questions

Cirrhosis affects more than 5 million Americans, of whom a substantial percentage is decompensated and requires frequent hospitalization. Several federally-funded studies have demonstrated an unacceptably high rate of readmission in this patient population. These readmissions are a tremendous medical, psychosocial and financial burden on patients, caregivers and society. Studies have identified consistent preventable risk factors that can be targeted to prevent these readmissions in cirrhotic patients. However, the dissemination of this information into practice using interfaces that improve patient-caregiver and clinician interaction through mobile health technology is limited. The active participation of the caregivers, who are deeply involved in the care of these cognitively impaired cirrhotics, also needs to be further explored to prevent these readmissions.

Patients with cirrhosis are prone to clinical and psycho-social issues that manifest as patient-reported outcomes (PRO), which can independently predict hospitalization, re-hospitalizations and death. Our group has studied the impact of these PRO extensively. With the increasing spread of health-related electronic devices, the relevance of health IT in the management of chronic diseases such as cirrhosis is paramount. The team has already developed and used several health IT advances to educate patients and their caregivers in inpatient and outpatient settings. These tools include Patient Buddy to prevent avoidable readmissions and EncephalApp Stroop to detect and guide therapy for cognitive dysfunction in cirrhosis. However the evaluation of these tools in a multi-center study that adapts to the status of the patients and their caregivers is required.

The central hypothesis is that cirrhotic patients randomized to health IT interventions that elicit PROs in a structured outpatient setting will have a significantly greater reduction in hospital readmissions because of improved communication with their medical teams compared to standard of care regardless of scheduled return outpatient visits.

Patient Buddy™ is an innovative application that is HIPAA compliant and adaptable to specific patient populations. It includes the ability to securely integrate with hospital based systems or work in a HIPAA compliant hosted environment with separate patient and caregiver interfaces focused on several aspects that impact re-hospitalization. Specifically, it has the ability to record vitals, cognitive performance, questionnaires, medication dosages and intake and can communicate with the clinicians and pharmacies. Patient Buddy has been developed by our technology partner, Creative Information Technology, Inc. (CITI).

Given this immense gap in our knowledge regarding the use of patient and caregiver-centered interfaces in the prevention of re- hospitalization, our hypothesis is that Patient Buddy, a mobile patient-caregiver-clinician interface, will effectively reduce readmissions in decompensated cirrhotic patients within 30 days of discharge.

We plan to follow three groups of cirrhotic patients from the time of hospital dismissal randomly divided into either receiving standard of care, using devices through which they can communicate with the clinical teams and using devices and structured follow-up over thirty days. Our aim is to develop these devices so as to learn quickly about issues that patients and their caregivers are facing so that we can intervene to stop unnecessary and re-hospitalizations in this population.

2. Describe the study's specific aims or goals.

Specific Aim 1: To evaluate in a multi-center, randomized trial the effectiveness of (patient reported outcomes) PROs elicited using PatientBuddy and EncephalApp Stroop with and without scheduled outpatients return visits on the prevention of avoidable 30 day readmissions in patients with cirrhosis and their caregivers compared to standard of care.

As part of this specific aim, we will include 450 total cirrhotic patients and 450 caregivers (150 patients and 150 caregivers per center), who will be followed for 30 days post-discharge. The groups will be randomized 1:1:1 into a standard of care group, a group receiving health IT interventions who will receive PatientBuddy and EncephalApp Stroop with as-needed follow-up and another group that receives the same health IT interventions along with scheduled outpatient visits and calls within 30 days of discharge. Avoidable readmissions will be adjudged using a blinded adjudication committee and the differences between the three groups will be compared.

The Health IT groups will be given iPhones loaded with the Patient Buddy app with caregiver and patient interfaces. They will be instructed extensively regarding the use of the App, which is preloaded with variables that associated with readmissions such as medications and adherence, issues with cognition and orientation and new symptoms. The patient and the caregiver will have separate devices linked to a device with the nurse coordinator through which daily communication will occur between patient/caregivers and the study team regarding previously identified risk factors associated with readmission. With this enhanced communication and educational value of the App, the study team will have greater access to events at patients' homes and the potential to prevent readmissions by intervening at that stage. The team will also engage the end-users (patients, caregivers and the nurse coordinator) by inquiring about their input in order to enhance the interface, user-friendliness and impact of the App. A detailed analysis of 30-day readmissions, including potential preventability with Patient Buddy will be performed. CITI will be responsible for establishing and monitoring the communication channels and implementation of the interfaces.

For Peer Review

Specific aim 2: To incorporate the opinion of key stakeholders (patients, caregivers and nurse coordinators) towards improving the Patient Buddy App in the prevention of readmission in cirrhosis

The input of patients, caregivers and nurse coordinator and analysis of potential preventability of readmissions in specific aim 1 will be used to enhance the Patient Buddy App.

3. Describe the study's background and significance, including citations, or upload a citation list in document upload. Use lay language whenever possible.

1. Significance of the problem of cirrhosis and hospitalization

Cirrhosis affects more than 5 million patients in the United States1. The natural history of cirrhosis involves a compensated and a decompensated phase2. Decompensated patients develop complications of cirrhosis such as hepatic encephalopathy (HE), ascites, variceal bleeding, infections and spontaneous bacterial peritonitis (SBP). These complications led to more than 1.5 million hospitalizations and cost nearly $4 billion yearly3.

2. Readmissions in cirrhotic patients are an unresolved burden

Despite readmissions within 30 days being a quality improvement issue, there have been several federally-funded studies that have shown a relentless increase in this rate4. The 30-day readmission rate for cirrhotic patients is as high as 37% in prior NIH- sponsored studies from multiple centers in North America5-7. This was associated with a significantly higher 90-day mortality compared to subjects free of 30-day readmission. Therefore readmissions are an unresolved burden on the patients and the medical system.

3. Factors associated with readmission can potentially be modified

Studies from our group and several other groups have demonstrated that specific cirrhotic subgroups are particularly vulnerable to readmission5-8. A large proportion of these factors are modifiable with poly-pharmacy, lack of understanding of medication use and their adverse events being primary issues . Patients are often re-admitted for HE, falls, infections and ascites-related issues5, 8-10. However despite the knowledge, there is poor dissemination of these findings into practice in order to prevent readmissions.

4. Caregiver engagement in the prevention of readmission is poorly studied in cirrhosis

Since most studies have concentrated on the individual patients' understanding of their disease process and their medications, the role of the caregiver/companion during this process has not been well studied. The involvement of the caregiver is a critical piece of the puzzle because patients with decompensated cirrhosis have cognitive dysfunction due to minimal or overt HE that can impair judgment and memory and are often unable to perform instrumental activities of daily living11. This can impact their daily function, development of future complications and socio-economic status from an individual, family and societal basis12-14. Therefore, caregivers are essential to the understanding of the disease complications, prevention of medication-associated issues and to alerting relevant clinicians earlier to manage problems as an outpatient, which if neglected could lead to readmission. Studies have shown that caregivers of cirrhotic patients are deeply affected by this disease from a psychosocial and financial perspective but they are often not involved while the disease severity, progression and complications are being explained to the patients15-17.
The absence of caregiver involvement in the previous studies of readmission prevention is a major gap in our knowledge which requires investigation.

5. Current methods of preventing readmissions are inadequate and are reactive instead of pro-active

The current standard of care in cirrhosis at this time is to schedule appointment follow-up and occasional telephone calls to the patients directly5. There is little systematic investment into engaging the patient/caregiver dyad proactively and disseminating knowledge. The system thus is only geared towards evaluating patients when the problem requires emergent or urgent visits18. Therefore current knowledge that could prevent these readmissions is inadequately disseminated to the affected parties with the current standard of care.

6. Mobile health applications are required to engage patients and caregivers with clinicians

The rapid dissemination of multiple studies that clearly define preventable reasons for readmissions in cirrhosis requires direct modes of communication between clinicians and the patient/caregiver dyads19. Mobile health apps which are able to communicate problems that can be handled before they need an emergent visit to the hospital are therefore a potential method to prevent these readmissions.

7. The conclusion from the original proof-of-concept study : "patient buddy app for prevention of readmissions in cirrhosis patients",showed that the use of the Patient Buddy app is feasible in recently discharged patients with cirrhosis and their caregivers. Eight HE-related readmissions were potentially avoided after the use of the App. (Note abstract uploaded in documents section) Standard of care follow-up post discharge is 4 weeks (30 days) minimum and possibly 2 weeks depending on the reason for admission, based on the results of our pilot study. Since we noted poor adherence with the fall -risk assessment and daily sodium intake in the previous pilot version of the Buddy App Study, both have been removed in the RCT version of this study."

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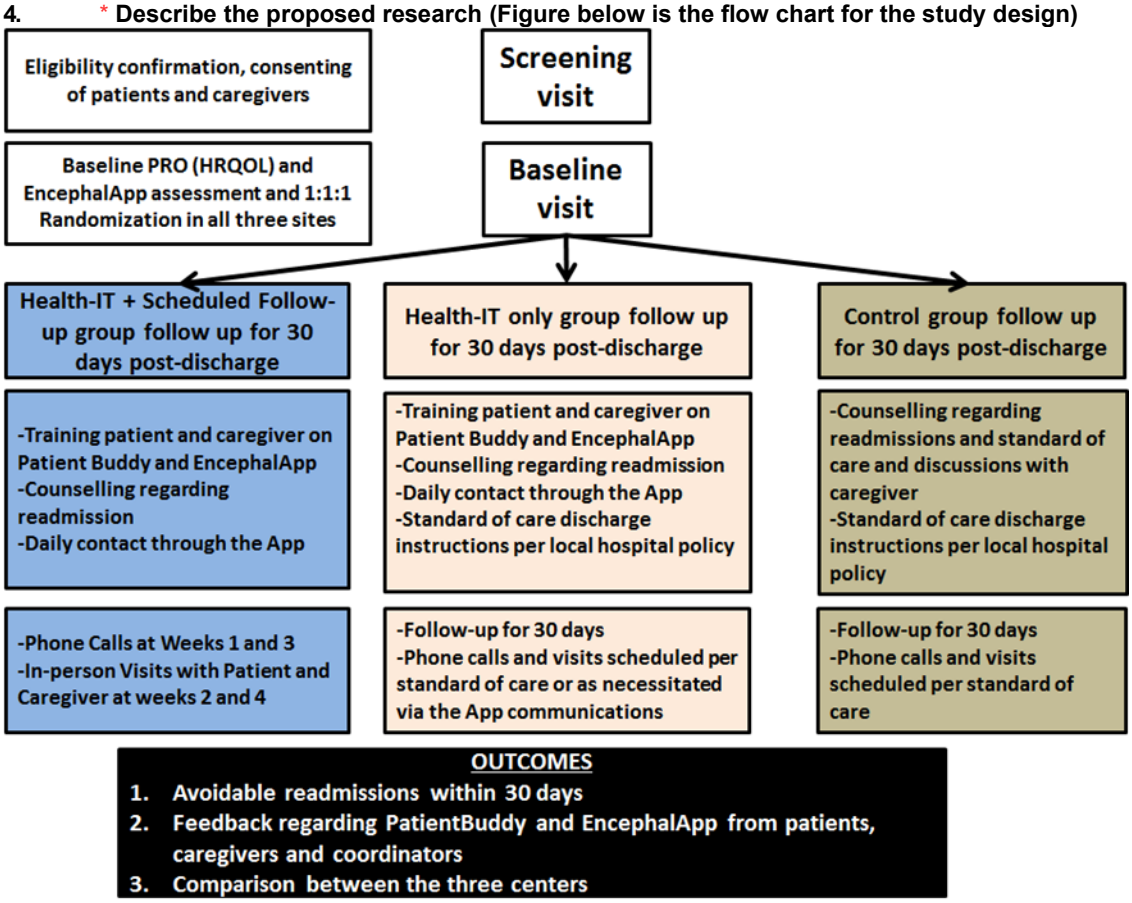
4. * Describe the proposed research (Figure below is the flow chart for the study design)



Recruitment of Subjects and Informed Consent Process: Subjects will be recruited from the Inpatient Service at VAMC. Each morning, the CITI-trained nurse coordinator (who will also act as the nurse coordinator) will check with the inpatient attending if cirrhotic subjects have been admitted. These subjects will be reviewed by the PI and/or co-investigators. If they appear to be reasonable candidates, the coordinator and investigators will discuss the study with them and their caregivers. Sufficient opportunity will be provided to them to have all their questions/concerns answered before consent will be obtained. If subjects and caregivers are agreeable, study activities will start at the day of discharge. All female patients of reproductive age group will undergo a urine pregnancy test.

After informed consent is obtained from both patient and the caregiver separately, we will administer the EncephalApp Stroop to the patient. EncephalApp Stroop is a validated cognitive test that takes 5-10 minuteto perform, which can give valuable information regarding the cognitive flexibility and psychomotor speed of the participant. This has an easier Off State and a more difficult On state. The ultimate outcome is the time taken to complete both Off and On states in seconds known as OffTime+OnTime. The EncephalApp Stroop will be administered by the study team to patients at baseline and at study end in group 1. For those randomized to group 2, it will be administered at baseline to the patient by the study team and then will be taught to the caregiver to administer weekly or if the subject has any issues. Like in group 1, all patients will undergo this again at study end.

Training will be given to all patients and caregivers regarding (a) cirrhosis (b) hepatic encephalopathy (c) ascites and low-sodium diet and (d) individual medication evaluation, using printed standardized patient information handouts from UptoDate. We will answer all questions raised by the patients and caregivers and the team will also individualize training based on the specific reason for admission.

We will then proceed with 1:1:1 site-specific randomization in blocks of 4 using a random number generator overseen by the statistician that will be communicated to the sites beforehand.

Group 1: Standard of care group:

Dyads randomized to the control group will be discharged per local hospital policy with instructions from their team. They will be given the contact number of the study team to call as needed and will then be seen at day 30 of an in-person visit. We will follow the medical record of the patients to evaluate for intervening readmissions but will not call them specifically. The standard of care of these patients is usually either follow-up as needed or occasional phone calls as needed by the clinical team. The standard of care also depends on the acuity of the presentation and the ability of the patient to follow-up. For this study, we will require a 30-day visit from the patient and caregiver.

Group 2: Health-IT only group:

Training at the time of discharge: The Patient Buddy app with preloaded caregiver and patient interfaces will be shown to the subjects and caregivers with detailed instructions including: User Guide of Patient Buddy, Quick Reference Sheets for Case Coordinator to give the Patient and Caregiver with screenshots and tips and tricks for maneuvering around the modules, Powerpoint presentation that goes through the workflows for patients and caregivers, and one on one training for the Case Coordinator given by the CITI Representative. In addition, administration of five orientation questions (what is the date, what is the time, what is the year, who am I and where are you?) and EncephalApp Stroop will be taught to the caregiver. The call-in numbers for the nurse coordinator, GI physician on call and the contact information for the

principal investigator will also be programmed into the app. A detailed training session will be performed over the next hour by the coordinator and the PI to both the patient and the caregiver. This training will be tailored to the specific issues faced by the patient while they were hospitalized. The individualized login and passwords for each patient and their caregiver will be established and given to them. A copy will be kept with the nurse coordinator in case the subjects forget their codes. These will be reset upon return of the devices at the end of the study. The connectivity and messaging system in-built into the Patient Buddy App will then be checked and the control center of the CITI communications notified of this enrollment. This will also be checked by sending messages by the patient and caregiver through the App to the coordinator and the PI (Figure 3 demonstrates the data flow). In the health-IT only group, there will be daily contacts between patients, caregivers and the clinical teams via the App. The only visit scheduled for the study will be at day 30 when the study will be completed. However, if there are issues that come up during the intervening period detected via the App, the clinical team will reach out and determine with the patients and caregivers if an ad hoc intervening visit is required. The team will not meet with patients or caregivers if they are scheduled to be seen as standard of care in their clinics in between the 30 days unless specifically required by the symptoms or if the patient requires readmission. If the patient requires readmission before day 30, their participation will end at that time.

Group 3: Health-IT+Scheduled Follow-up Group:
This group will undergo the training at discharge similar to what was performed in group 2 but we will also intersperse the 30 day follow up with one visit and 2 scheduled phone calls as below. Visit Scheduled: Patients and caregivers will be formally called at day 7and 21 post discharge by the study team to inquire about issues that were not communicated via PatientBuddy. We will also perform a study visit at day 15 and day 30 with both patients and caregivers to define any new changes in the patient's condition, elicit feedback throughout the process and at the day 30 visit, returning the devices and resetting them. No additional charges will be generated from the study during these visits.

The week 2 visit will include vital signs as well as the discussion of any issues with the buddy app, patient medication update, and any new medical issues. The subject will also be given the EncephalApp stroop and orientation test for the week like in group 2. Study staff may also observe the caregiver and subject perform their daily app entries. (subject may document medications taken, abdominal girth measurement, and daily weight. The caregiver may document medications, daily weight, abdominal girth, orientation questions and stroop test) The study staff will offer guidance as needed to complete these tasks. If the patient has a >10lb weight gain from baseline, a >5 inch girth increase, and/or is febrile, the study team will notify the hepatologist on service and the PI for direction. No blood will be collected for the study and/or tests run for study purposes at any time. However, if the subject is febrile, has overt encephalopathy, is bleeding, and/or is more decompensated, the study team will alert the medical team and coordinate care as needed. Any care performed as a result of the findings from this visit will be conducted per standard of care by the medical team."

FOR GROUPS 2 AND 3: If the subject is re-admitted, they meet the endpoint and their participation will end. We will contact the caregiver and coordinate a return of the smartphones and end of study elements. We will also request a discharge summary from the outside hospital if they were hospitalized outside of McGuire VAMC. If the patient is in-house, we will coordinate the end of study while in the hospital if appropriate. The phones distributed to the participants in groups 2 and 3 are not capable of making phone calls and have a restricted data plan under CITI. Only data entered in the Patient Buddy App will be transmitted directly to the HIPAA-compliant CITI server. At the end of the study (at day 30 or readmission within 30 days), the phones will be turned in and remotely wiped of any data. Therefore, any other data generated (browsing, photographs etc) performed by the patient/caregiver on their phones will be wiped without transmitting over to any other entity. Therefore, there are no privacy or confidentiality risks pertaining to this.

Patient Buddy App Use (for groups 2 and 3): The Patient Buddy App will be loaded onto the phones given to the patients and caregivers by the study team with the following data and the instructions to get in touch with the team (Table 3)

Contact through Patient Buddy
- Daily contacts pertaining to adherence, cognition and measurements as needed (details below)

Unscheduled contacts:
- If nothing is entered in the Patient Buddy for>24 hours by either patient or caregiver
- Depending on results of scheduled telephone calls
- Admissions to McGuire VA medical center or after discharge from other hospitals if admitted
- Telephone calls generated from patients/caregivers to the study team

"The study team will reach out to the patient with an open statement such as :"hello_____we noticed you have not recorded anything today, is everything ok...any questions? ' The app will be checked by the study team every day. Since the subjects have multiple medical problems and their questions are not uniform, the study team will not have a standardized set of responses; they will utilize their medical training to address questions appropriately and in the event of progressive decompensation, will alert the medical team and PI and coordinate urgent care. Any care performed as a result of the findings from these communications be conducted per standard of care by the medical team." Subjects will also be given the number (as is standard of care) for the GI-physician on call and will also be able to call emergency services if they are not able to wait to use Patient Buddy.On the day of discharge, the study coordinator, patient, caregiver and the case coordinator will meet for the training and evaluation of the Patient Buddy App as well to check the connectivity.

The following data will be collected and reiterated to the patient and the caregiver (Table 3).

Table 3: Patient/Caregiver Logs into the buddy at home daily and to contact study team

Area of interest	Specific entry in Patient Buddy	To contact study team, GI physician on call or emergency services(marked*)
Medication adherence on each medicine on discharge	Enter each medicine administration time, date and dose	Questions regarding medications, missing or increasing dose
New medications and supplements	Enter new medicine and dose	Call when a new medicine/ supplement is initiated

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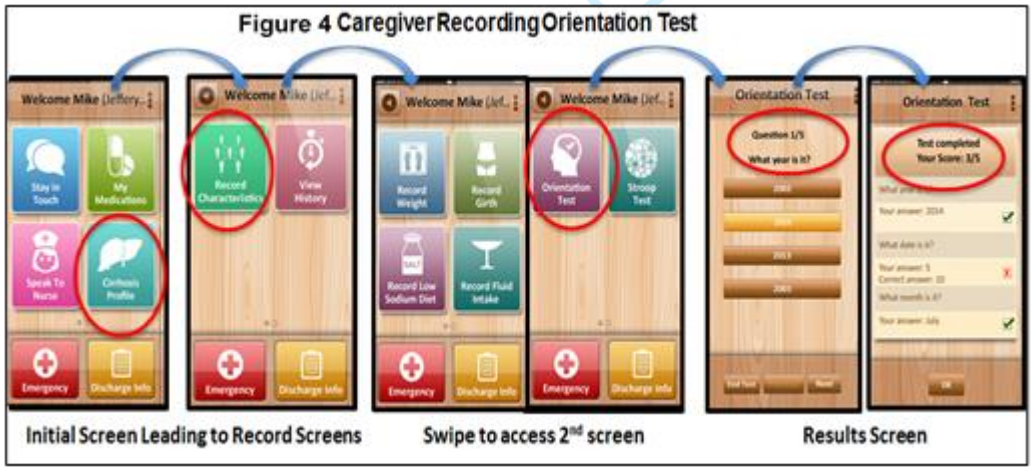
Vitals (to be taken at same time every day)	Daily weight	≥3 lb increase in 24 hours
	Daily Temperature	> 100.4 F or < 96.8 F
Cognition (assessed every week or when caregiver feels patient is not acting normally)	Orientation questions (5 questions time/place/person)	Any question abnormal, coma*, confusion, or difficulty waking patient up*
	EncephalApp Stroop Score	>25 seconds over discharge score(15)
	Daily bowel movements	<3 or >6 bm/s day (if on lactulose) and any change in those without lactulose
Emergency/urgent/other symptoms	GI bleeding (detailed symptoms noted)	Black stools, red blood in stools or vomiting blood*
	Infections (detailed symptoms noted)	Fever, shortness of breath, burning in urine, abdominal pain, nausea or vomiting

The data collected from each patient's medical chart to meet enrollment criteria for this study at discharge will be the discharge summary, contact information, and all elements to verify inclusion/exclusion criteria (no substance abuse, >21 years of age, non-elective hospitalization, will be discharged home, no dialysis) Also, if the patient is re-admitted, discharge summary will again be collected.

Training and counseling at the time of discharge: The Patient Buddy app with preloaded caregiver and patient interfaces will be shown to the subjects and caregivers with detailed instructions. The call-in numbers for the nurse coordinator, GI physician on call and the contact information for the principal investigator will also be programmed in to the app. A detailed training session will be performed over the next hour by the coordinator and the PI to both the patient and the caregiver. This training will be tailored to the specific issues faced by the patient while they were hospitalized. The individualized login and passwords for each patient and their caregiver will be established and given to them. A copy will be kept with the nurse coordinator in case the subjects forget their codes. These will be reset upon return of the phones at the end of the study. The connectivity and messaging system in-built into the Patient Buddy App will then be checked and the control center of the CITI communications notified of this enrollment. This will also be checked by sending messages by the patient/caregiver through the App to the coordinator and the PI.

The Patient Buddy App will be loaded onto the Phones given to the patients and caregivers by the study team with the following data and the instructions to get in touch with the team.

The Patient and Caregiver Patient Buddy Initial Screens after Login are shown in Figure 4



The caregivers and patients will independently log in and provide updates as needed on action items that lead from each icon. All important items in the discharge counseling are in the home screen for patients and caregivers.

Role of caregivers:

Caregivers will be given instructions on cognitive testing and EncephalApp Stroop testing and the use of the weighing machine and tape measure for measuring weight and abdominal girth respectively. Caregivers will be instructed to give the orientation questions and EncephalApp Stroop to the patient if they appear not behave normally or once per week after discharge.

EncephalApp is a validated test of cognitive functioning in cirrhosis, which consists of an easier Off state and a harder On state. The respondents have to correctly identify the color red, green or blue in presented "#" symbols during the Off state while in the On state they still have to pick the correct color from words presented in a discordant color. E.g. the word "GREEN" will be presented in a blue color and the correct answer is blue not green. There are 2 training runs for each state and the patient has to complete 5 complete runs in both states. The total time to complete 5 runs in the Off and 5 runs in the On state is the "OffTime+OnTime" which is noted in the Patient Buddy App once this is presented to the patient every week by the caregiver.

While we aim to prevent all readmissions, the focus is to disseminate information through Patient Buddy on three specific preventable areas that are responsible for a majority of readmissions:

(A) Hepatic Encephalopathy, (B) Ascites and fluid/electrolyte management (C) Infections

The following will be performed jointly between caregivers, patients and study team to prevent readmission. Prevention

of recurrent episodes of hepatic encephalopathy:

- Ensure patients are started on medications appropriately on discharge.
- Involve the caregiver at all levels of care, including cognitive/orientation testing as needed
- Ensure patients are taking the specific dose of medications (a) Reduce lactulose dose if patient is dehydrated (b) increase lactulose dose if patient is not clear mentally.
- Simple orientation questions and EncephalApp Stroop to gauge changes in cognition.
- Early clinic appointments to treat HE and prevent hospitalization or worsening of disease.

Management of ascites, fluid and electrolyte issues:

- Reiterate the dosage schedule of diuretics at discharge and daily entry of diuretic doses, weight and abdominal girth (example in **figure 6**)
- 2gm Na diet if indicated and daily charting of the adherence
- Stop diuretics and contact nurse coordinator in case the patient is dizzy or lightheaded

Prevention of recurrent infections:

- Adherence on antibiotics to complete therapy as needed and/or adherence on SBP prophylaxis
- Education of caregivers that HE could indicate infection.
- Call or alert team immediately if patient has fever, chills, nausea or abdominal pain

Figure 6: Nurse Manager Screens showing medication adherence

The nurse coordinator receives data continuously throughout the day, monitors all values from the patients and caregivers on their iPad. They will alert the patient/caregivers with alarm issues and contact the PI/ physician-on-call if urgent action is required. On the weekends and after hours, there will be coverage of the iPad with Dr Jawaid Shaw and Dr Acharya. As mentioned above, subjects and caregivers will again be told about the need to communicate urgent issues with the GI fellow on call rather than waiting for a response in the App.

The App gives caregivers and patients

A. An opportunity to directly communicate with the study team
B. Guidance as to when to call emergency services

No other medical information or advice is in-built in the App, but it largely forms a conduit between the study team and patient/caregivers.

The nurse study coordinators will regularly provide feedback to the app developers regarding the app. This feedback will be informal and will occur on a rolling basis. The nurse study coordinators will not be surveyed or interviewed formally. Unlike with the formalized patient feedback, we do not intend to generalize any findings from the nurses' feedback, and will solely use the information they provide for quality improvement of the app."

30 DAY VISIT FOR ALL GROUPS: All patients discharged from the hospital are scheduled for a 30 day follow-up at minimum as a standard of care visit. Some patients will be scheduled for a 2 week follow-up post discharge as standard of care, depending on the reason for admission. The medical team will collect labs, perform a physical exam, and provide routine care taylored to the individual patient and his/her medical issues on the day 30 visit. These procedures are all standard of care and are not done solely for research purposes. The study team will also meet with the patient and his/her caregiver at this day 30 visit and will not generate any costs for the pt. We will collect the smartphones and have the patient and caregiver complete a survey regarding their experience with the app. The pt and caregiver will be together. The questions to be asked are uploaded to this submission."

Decision regarding avoidable readmissions: This will be made by analyzing the discharge summary of the hospitalized patients and will be classified into avoidable or unavoidable by the committee with three hepatologists (1 each from the 3 sites). The decision regarding avoidability is based on the question whether could a clinic visit or earlier communication/education with patient and caregiver prevented this admission.

There is no specific hard and fast rule about which admissions are classified as one or the other, which is why a committee is necessary. On the whole, admissions for elective paracentesis, thoracentesis, early stages of hepatic encephalopathy etc are usually avoidable but those related to infections, severe hepatic encephalopathy, variceal bleeding etc are usually not considered avoidable. However, since each case is unique, all discharge summaries of patients admitted within 30 days will be sent to the committee to review and vote. The committee will not be told about the assignment of the patients.

SAEs: we do not anticipate SAEs i.e. re-admissions to be related to the App itself because that is what is the focus of the study. Therefore, SAEs simply associated with admissions will not be reported to the IRB. We do not expect other SAEs directly related to the App to appear in this study.

Active Data Collection

1. * **Describe the technology chosen for collecting the data and transmitting data securely over the internet. Give the rationale for selecting this technology:**

For groups 2 and 3, we will use the Patient buddy app. This has been described in great detail in the uploaded grant but the details are below. **Patient Privacy and Security**: The App is HIPAA compliant with federal regulations regarding Privacy andSecurity. Patient Buddy is considered a Business Associate under the terms of the final HIPAA Omnibus rule. The data management of this study will operate using a secure hosted environment with a HIPAA compliant server and data storage network. Given the sensitivity and need for security in managing and handling personal health information, Patient Buddy has developed its application such that no data are stored on either any of the distributed devices. Only after verification and authentication of login credentials is established with the server, is any data pushed out to the appropriate devices. All data are transmitted to the server where they are controlled behind the network firewall.

Patient Buddy Design to Protect PHI: The Patient Buddy App will be hosted at a secure data center using a HIPAA compliant server. The data center provides several key security features that contribute to the safeguarding of PHI. These data safety and security features include physical security of the data center and infrastructure; perimeter security of IP reputation; network security for intrusion detection, firewall and vulnerability; server security for OS, anti-virus and log management; along with procedures and protocols for data backups, security audits, access control, change controls, and the maintenance of policies and procedures. From an application and program management standpoint, Patient Buddy offers further security safeguards to protect PHI to include secure data deletion upon termination of services; administrative security that provides for secure access and two-factor authentication; program access control; security policies and procedures, incidence response protocols, and risk assessments monitored and updated by our privacy and security officer, as well as data management and application management processes. All Integration of exports from the EncephalApp Stroop test will be handled with the same security and privacy concerns. At no time will any PHI be disclosed and all data will be filtered through the HIPAA compliant servers. Data Integration: Regarding the architecture, Patient Buddy's server application is responsible for the data interchange between the database and the mobile apps. This can also serve as the integration point with EHR's and third party vendors. The Database uses Microsoft SQL Standard Enterprise version and it is hosted on virtual machines to reduce deployment time. CITI also uses caged physical servers deployed in geo redundant locations.

2. * **Describe how data will be linked or unlinked to identifiers including email addresses, names, and/or IP address.** No identifiers are in the App or smartphones or iPads

3. * **Is there an alternative method for completion of the data collection other than the internet:**

No

4. **If yes, describe the alternative(s):**

The Health IT component is the entire focus of the study; inability or not wanting to use Apps are an exclusion

5. * **Describe how individuals will be able to skip or not answer particular questions. If any questions are mandatory, provide justification:**

There are key questions related to
a. Medication adherence
b. New medications
c. Vitals
d. Cognitive testing

Are all essential and will be queried if not entered. These are important because these are the leading causes of avoidable readmissions and are therefore mandatory.

Data Confidentiality and Storage

Confidentiality refers to the way private, identifiable information about a participant or defined community is maintained and shared.

1. * **Specify where this study's paper and electronic research data and/or physical specimens will be stored and how they will be**

secured from improper use and disclosure:

We will keep all data private by only using study IDs on the patient's paper charts and also storing all information on a secure, password-protected drive. The charts will be kept under lock and key in the offices of Dr Bajaj and Ms Gavis and Yost which are only accessible to the study team. The password protected drives will only be accessible to the study team.

Patient Privacy and Security: Patient Buddy™ is HIPAA compliant with federal regulations regarding HIPAA Privacy and Security. Patient Buddy is considered a Business Associate under the terms of the final HIPAA Omnibus rule. The data management of this study will operate using a secure hosted environment with a HIPAA compliant server and data storage network. Given the sensitivity and need for security in managing and handling personal health information (PHI), Patient Buddy has developed its application such that no data is stored on either any of the distributed devices. Only after verification and authentication of login credentials is established with the server,is any data pushed out to the appropriate devices. All data is transmitted to the server where it is controlled behind the network firewall.
Patient Buddy (App) Design and Implementation to Protect PHI: The Patient Buddy App will be hosted at a secure data center using a HIPAA compliant server. The data center provides several key security features that contribute to the safeguarding of PHI. These data safety and security features include physical security of the data center and infrastructure; perimeter security of IP reputation; network security for intrusion detection, firewall and vulnerability; server security for OS, anti-virus and log management; along with procedures and protocols for data backups, security audits, access control, change controls, and the maintenance of policies and procedures. From an application and program management standpoint, Patient Buddy offers further security safeguards to protect PHI to include secure data deletion upon termination of services; administrative security that provides for secure access and two-factor authentication; program access control; security policies and procedures, incidence response protocols, and risk assessments monitored and updated by our privacy and security officer, as well as data management and application management processes. All Integration of exports from the EncephalApp Stroop will be handled with the same security and privacy concerns. At no time will any PHI be disclosed and all data will be filtered through the HIPAA compliant servers.
We will provide feedback on app usability with CITI quarterly by sending them a de-identified spreadsheet with survey results.

2. * **Who will have access to study data:**
Only the study team will have access to the data only

3. * **If the study will code (i.e. de-identify) the research data by replacing subjects' names with assigned subject IDs, explain the following aspects of the coding process:**

The codes will be assigned with subject sequential number, date of enrollment and whether this is a patient or a caregiver. The key will be kept on a secured hard drive accessible only to the study staff and will be destroyed after the minimum data retention period is over

Non-VA Site Details* How will communication occur between sites for discussion of study conduct, unexpected problems, project modifications, and interim results:
A hepatologist study investigator will be selected to represent each of the three study sites. A conference call will be held quarterly and the 3 site selected investigators will review and discuss the de-identified data to determine if any re-admissions could have been prevented. As questions and issues occur, the same group will be the conduit to problem solve as a group and keep the study team informed.

Study Population

1. * **Provide the total number of individuals at VAMC:** 300

2. **If this is a multi-Center Project, what is the total anticipated number of subjects across all sites:** 900

3. * **Provide justification for the sample size:**
Sample size: Prior studies and our cohort have shown a 30-day readmission rate around 33% using current practice, and of which 20% were considered avoidable. Per our preliminary data, the rate of 30-day avoidable readmission reduced to 5%. However, we will be circumspect and increase this relative avoidable readmission rate to 9%. In order to determine a similar reduction at 80% power at an $\alpha = 0.05$ level of significance we would require 45 patients in the Health-IT+scheduled visits, 45 patients in the Health- IT only and 45 patients in the standard of care group per site leading to a total of 135 patients per site or 405 total patients. This will also include 405 caregivers. Allowing for a 10% dropout rate, we plan to we will enroll a total of 450 patients, of which 150 will be randomized to health-IT+scheduled visits, 150 to health-IT only and 150 to standard of care across all three sites. This will be accompanied by an equal number of the respective caregivers bringing the grand total of subjects across all three sites to 900.
Therefore at McGuire VAMC we will enroll 50 patients and 50 caregivers in each group for a total of 300 subjects (150 patients and 150 caregivers).

4. * **List the study inclusion criteria:**
Cirrhosis patients ≥21 years of age hospitalized for non-elective reasons
•Adult caregiver and the patient living in the same house
•Both (caregiver and patient) should be able to complete the Patient Buddy training and evaluation
•Discharged home from the hospital
•

5. * **List the study exclusion criteria:**
- Elective hospitalization
- Lack of an adult caregiver

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- Active alcohol/substance abuse within 1 month of the hospitalization
- Unable to perform training or give consent
- Patients discharged to hospice, nursing home or extended care facilities

Patients on Hemodialysis
pregnant women
patients with limited English proficiency

Potential Subject Identification and Recruitment

There will not be any special recruitment flyers since all patients will be hospitalized at VA and will be enrolled through direct contact after referral or by reviewing the inpatient lists for potentially eligible patients.
Subjects will be recruited from the Inpatient Service at VAMC. Each morning, the CITI-trained nurse coordinator (who will also act as the nurse coordinator) will check with the inpatient attending if cirrhotic subjects have been admitted. These subjects will be reviewed by the PI and/or co-investigators. If they appear to be reasonable candidates, the coordinator and investigators will discuss the study with them and their caregivers. Sufficient opportunity will be provided to them to have all their questions/concerns answered before consent will be obtained. If subjects and caregivers are agreeable, study activities will start at the day of discharge

Privacy

Before approaching the patients and caregivers, the study team member will make sure that the conversation cannot be overheard and will get a private setting in the inpatient unit. This maintenance of privacy will continue throughout the process of study conduct and data dissemination and during the contact between study participants and the team during the 30-day follow-up period.

Costs to Participants: no specific study related costs to the patients or caregivers.

All medical care provided for the study participant will not be study related, but standard of care.
The medical team following the study subject as a patient in clinic at week 2 (group 3) and day 30 (all groups) may perform the following procedures as standard of care:vital signs to include BP, HR, Temperature, height, and weight. The medical team may also send the following labs as standard of care: CBC with diff, comprehensive metabolic panel, liver panel and pt/inr. All of these procedures will not be covered by the study and will be charged to the patient's insurance company. Since the medical procedures needed for pt care will be as standard of care, the current process of determining medical coverage

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will be used.

Compensation

1. If the patients and caregiver dyad completes the study 30-day follow-up (or are hospitalized in between, which will end their study participation), we will provide them a check for $100 for the patient and $75 for the companion for a total of $175 for the study participation.

2. **If compensation will be pro-rated, explain the payment schedule:** No pro-rated compensation will be provided.

Risks, Discomforts, Potential Harms and Benefits

1. * **Describe the risks of each research procedure to participants or others.**

1. Physical risks: none from the use of the app.

2. Psychological/social risks: Very small risk of loss of confidentiality and privacy. They may feel anxious about completing the cognitive tests especially if they notice a decline.

3. Financial risks: since groups 2 and 3 will be in greater contact with their care team, they may be referred to their medical team for treatment or medication changes (for example), which may result in unanticipated costs for the participant.

2. * **Describe how the risks / harms will be minimized:**

1. Psychological/social risks: Very small risk of loss of confidentiality and privacy. Privacy and confidentiality will be maintained at all levels by only consenting patients and caregivers in a private setting even when hospitalized at the time of enrollment. Patient and caregivers will be given separate smart phones with separate login information that does not contain any PHI. The login information copy will also be kept with the nurse coordinator in case the patients/caregivers forget them and needs to call the coordinator.
None of the devices has PHI stored in them and using the HIPAA-compliant servers, all data will be pushed onto the servers when entered. In case the smartphones are lost, misplaced or stolen, therefore there is no risk to PHI. Important to note is that there is no PHI stored on the any devices and therefore misplacing a device will not compromise patient data integrity. All data is pushed out to the device once login has been authenticated. First login is established after a two-factor authentication challenge is completed.
Once done, the patient is able to set a user and password for subsequent logins. All data resides on a HIPAA compliant Patient Buddy server which offers its own set of data security protections and backup. In the event a device is lost or stolen, no PHI data will be compromised. Our budget for PatientBuddy includes support for extra devices that will be made available to patients that lose or break a device with minimal disruption expected to the study and replaced in an unscheduled visit. Breaches in data security, although not expected given that no PHI resides on the phone, will be reported to the patients and caregivers within 24 hours of us receiving any such information from CITI. This will also be reported to the IRB and an urgent conference between the study team and CITI will occur to assess the root cause and prevent future episodes.All data will be de-identified for analysis.
They may feel anxious about completing the cognitive tests especially if they notice a decline. .Since hepatic encephalopathy is a major reason for admissions, this cognitive testing tool is a critical tool for the study. Therefore If we find a participant is unwilling to use this app feature, they will be excluded.

2. Financial risks: since groups 2 and 3 will be in greater contact with their care team, they may be referred to their medical team for treatment or medication changes (for example), which may result in unanticipated costs for the participant. Although we will discuss these issues with our subjects at consent, we will also note being admitted to the hospital is a larger cost that may be avoided.

3. **Where appropriate, discuss provisions for ensuring necessary medical, professional, or psychological intervention in the event of adverse events to the subjects:**
The process for addressing any significant subject reported medical issues through the buddy app is as follows:
The Buddy App will be checked throughout the day by the study coordinator. When a subject or caregiver notifies the study coordinator that he/she is having problems or questions, the coordinator will provide answers and support within his/her scope of practice. However, if the issues are more complex and need a physician's oversite, he/she will contact the PI and/or the medical team for direction. The medical team may chose to call the subject/caregiver directly, or may give the coordinator instructions to give the subject/caregiver. The coordinator will then contact the subject/caregiver with this information (and will document the instructions) The coordinator will also follow-up later to check on the subject and determine if the issue is under control/resolved.
If the issues are more complicated and the medical team wishes to examine the subject or feels the subject needs an outpatient intervention such as a paracentesis, the coordinator will facilitate a clinic appointment with the medical team in clinic and will check on the patient/caregiver and update any changes in care and/or medications in the buddy app.
In regards to answering your question re. what the medical team will do, this will be tailored to the needs of the patient/subject and will be different for each patient. Our hepatology patients with cirrhosis have many clinical problems and are frequently followed in clinic for labs, ultrasounds, paracentesis, medication adjustments, etc.

4. * **Describe any potential for direct benefits to participants in this study:**
Patients with cirrhosis and their caregivers suffer from several issues that can lead to multiple readmissions. Most of these issues are

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preventable by improving communications between patients/caregivers and the clinicians through intuitive mobile health applications. Therefore the use of Patient Buddy app and its streamlining using the pilot study is a critical step in empowering patients and caregivers in communicating with the team and preventing expensive and often unnecessary readmissions. Therefore this research is very useful for patients, caregivers, health care workers and potentially for society.

5. * **Describe the scientific benefit or importance of the knowledge to be gained:**
Readmissions in decompensated cirrhosis are a significant unresolved burden that affects more than 1 million patients and caregivers throughout the US. Prior federally-funded research clearly shows preventable reasons for these readmissions that need to be disseminated to the clinicians, patients and caregivers. Utilizing the secure Patient Buddy App to serve as a portal of communication and education between patients/caregivers and clinicians will serve as a platform for future research focused on prevention of cirrhosis readmissions.

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Buddy App Protocol changes

Protocol Amendment 1

Changes to exclusion criteria: edit existing criteria to allow alcohol use within one month provided subject has not had alcoholic hepatitis within 1 month; allow subjects on hemodialysis

Justification: To increase generalizability

Protocol Amendment 2

Due to COVID-19 related gap in enrollment, funding shortfalls, and low likelihood of us reaching the original study goals, a re-evaluation of the data was done to see if we could combine the two health-IT groups. Avoidable readmissions were similar across the 2 health IT groups and therefore, instead of 1:1:1 randomization, this was changed to 1:1 randomization with a total of 464 subjects (232 patients and 232 caregivers).

Justification: reduced enrolment requiring combination of the groups.

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