Title of the Study :

A Randomized, Parallel group, Pilot Study on the Effect of using the Portal724-Medication Electronic Medication System (MEMS) Smart Cap with Real-time Clinician Feedback on Medication Adherence Among Patients Infected with Chronic Hepatitis C (HCV) Being Treated with Grazoprevir/Elbasvir

Investigators :

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Introduction / Rationale of the Study

Hepatitis C and Adherence

Hepatitis C virus (HCV) infection is a very important health problem worldwide. Majority of the estimated 160 million people infected globally are unaware of their affliction [1]. It is a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. In the United States alone, HCV infection is the most common chronic blood-borne infection, affecting about 3.2 million individuals [2]. It is most prevalent among persons born from 1945-1965, most of whom acquired it in the 1970's and 1980's, since identification of HCV only occurred in 1989 as specific pathogen and blood products screening for the virus was non-existent [4]. Because at least 80% of those who acquire HCV will become chronically infected, it is the number one cause of chronic liver disease and liver cancer in the U.S. [3], and has surpassed HIV in terms of number of deaths [5] and the approximate U.S. economic burden is about $6.5 billion, inclusive of patients needing liver transplantation [2].

Steps have been taken to decrease this present and future healthcare and economic burden. Shortly after discovery of the virus, blood and blood-derived products started to be screened which led to a dramatic decrease in new incident cases. By 2001, the Needlestick Safety and Prevention Act was passed in the U.S., further deceasing new cases [7]. The CDC has also recommended a one-time screening for persons born between 1945 and 1965, as this segment of the population is at increased risk for HCV infection due to non-screening of blood products before 1989. Despite these measures, the Centers for Diseases Control and Prevention (CDC) estimates there are still about 17,000 new cases occurring yearly [3].

Treatment of HCV has been the main focus of clinical research since vaccine research has proved to be difficult, as well as the necessity of treating undiagnosed individuals. Among the 7 major HCV genotypes, genotype 1 is by far the most prevalent in Europe and in the United States. It has historically been the most difficult type to treat. Prior to 2011, the standard treatment for HCV was a combination of once-weekly injectable Pegylated Interferon with daily

oral Ribavirin to be taken for 48 weeks. The cure rate, measured as sustained virologic response (SVR) for this regimen is a dismal 40-50% [6]. Adherence to the treatment was difficult for many patients due to the length of therapy and the associated side effects of both interferon and ribavirin. The addition of new directly acting agents (DAA), Boceprevir and Telaprevir in 2011, revolutionized HCV treatment, increasing cure rates up to 75%. However, adherence continued to plague therapy because of side effects and thrice-daily dosing.

In 2013, 2 new DAA's were FDA-approved, ushering in the interferon-free era of HCV therapy. Sofosbuvir and Simprevir are once daily oral agents with much fewer side effects than any previous anti-HCV medication. Ledipasvir, another oral DAA, has been approved by the FDA in October 2014, to be given as a single tablet regimen together with Sofosbuvir. The length of treatment has also decreased, from 48 weeks to 12-24 weeks, and clinical trials of the combination of these drugs showed cure rates above 90%, with increased tolerability and safety [8]. Other DAA's since then have been approved by the FDA such as the combinations of ombitasvir/paritaprevir/ritonavir (Viekira Pak) and Grazopravir/Elbasvir (**Zepatier).**

are in clinical trials or under FDA review, increasing the chances that more patients can be cured from HCV infection.

Adherence, however, has been a major challenge in the treatment of Hepatitis C infection, especially before Sofosbuvir and Simprevir were introduced. Aside from side effects, Ribavirin has to be taken twice daily, while Interferon is injectable. Boceprevir and Telaprevir also had their fair share of side effects, drug interactions and multiple daily dosing which impaired treatment adherence. Studies on these medications have shown that the proportion of missed doses increases over time, and are associated with failure of treatment [11-14]. In one analysis of 2 clinical trials, patients who took their medications ≥ 80-85% of the time achieved SVR 86-90% of the time, while those < 80% adherent attained SVR only 8-32% of the time [28]. Aside from HCV medication-related issues, these patients may have other co-morbidities such as psychiatric disorders which can negatively influence patient compliance [18]. The matter of polypharmacy in patients co-infected with HIV and HCV can also be a major concern in terms of adherence [19].

Treatment adherence studies for Hepatitis C were mostly small studies of patients taking Pegylated-Interferon and Ribavirin [11-14]. These reports showed higher treatment success for patients who were at least 80-90% compliant, with most failures reported in patients with compliance rate around 70-80%. However, most of these also relied on patient self-reporting, pill counting and pharmacy refill data, which are inherently imprecise.

With the enhanced tolerability, lower drug-drug interactions, side effect profile and once daily dosing of the new DAA's, adherence has improved but is still an area of concern. In registration clinical trials, those who relapsed on Sofosbuvir were patients who did not comply to their treatment regimen [15]. The same holds true for Simeprevir, and these patients also developed resistant HCV [16]. With the standard 12-weeks course of these medications costing in the range

of $100,000 - $140,000, patients needing repeat treatment after relapsing can be very expensive [10], making treatment compliance even more important. It would also be very costly for treatment-experienced patients to be re-treated because of failure due to compliance.

We are conducting this study in the hope that we can ensure medication adherence to effectively and cost-effectively treat patients afflicted with chronic Hepatitis C infection. We have chosen HCV since the treatment is finite course (i.e. 12 weeks) which will enable us to measure the efficacy of using Medication Electronic Monitoring System (MEMS) with real-time feedback in terms of increasing adherence within a specific time limit. For this study, we are going to use **G**razopravir/**E**lbasvir **(**Zepatier), which has an inherent advantage of being a combination pill taken only once a day.

Medication Electronic Monitoring System (MEMS)

Medication Electronic Monitoring System (MEMS) has been used to measure patient compliance to treatment more accurately, especially in clinical trials. It has been determined to be a valid and objective tool to measure medication adherence [24]. Its use to improve compliance has been studied in patients with HIV [20-24], heart failure [26], smoking cessation therapy [27], and in the treatment of alcohol dependence [28]. A few studies have used MEMS in syringes and pill bottle caps to determine proper anti-HCV medication intake [14, 17], but data review and feedback to the patient were only done at each study visit. Real-time health care provider-to-patient feedback may be able to decrease non-adherence but robust studies in this area are still lacking.

There are several different types and manufacturers of commercially available MEMS. For this study, we are proposing to use the Portal724-MEMS Service. The Portal724-MEMS is a TURNKEY SERVICE. It integrates medication bottle, Smart Cap, Pill Dispenser, Embedded Computer, Embedded Cellular Modem and Tamper Proof apparatus. This device is capable of transmitting pill dispensing events from the patient's home to the Cloud over Cellular and IP networks. The transmission is done in real time if cellular coverage is above 1-bar, but if cell is not available or if the signal is below threshold, then the device Store-and-Forward feature is automatically activated.

The bottle cap records the number of Pill Dispenses, with date and time and Device ID. The purpose of this electronic monitoring is to estimate compliance with medication regimen.

Electronic assisted compliance is not the sole indicator of MEMS, it is also used in conjunction with answers about demographics, clinical state and symptoms to learn more about the patient characteristics that influence whether a medication regimen is adhered to.

Portal724-MEMS is HIPAA Complaint and ISO27001 Certified. The Electronic Data Capture, the Data Transfer and Data Access are all confidential and Secure in every stage of the Data

Flow Model. The device to be used in this study is a Smart Cap with Pill Dispensing and Integrated Cellular Modem.

Objective

Primary: To determine the effect of the use of Portal724-MEMS Service on medication adherence in the treatment of Hepatitis C patients with grazopravir/elbasvir with or without Ribavirin, defined as compliance to regimen 95% of the time.

Methods

Study design: Open-label, randomized, single center pilot study.

Treatment Arms:

Genotype 1a, treatment naïve or PegIFN/RBV experienced without baseline NS5A polymorphisms with elbavir/grazoprevir for 12 weeks

Genotype 1a, treatment naïve or PegIFN/RBV experienced with baseline NS5A polymorphisms with elbasvir/grazoprevir/ribavirin for 16 weeks

Genotype 1b, treatment naïve or PegIFN/RBV experienced for 12 weeks

Genotype 1a or 1b, PegIFN/RBV/PI-experienced with elbasvir/grazoprevir/ribavirin for 16 weeks

Genotype 4: treatment naïve with elbasvir/grazoprevir for 12 weeks

Genotype 4: PegIFN/RBV- experienced with elbasvir/grazoprevir/ribavirin for 16 weeks

Proposed number of participants: 40 patients infected with HCV (20 for each group)

Data Collection Time Period: approximately 1 year

Site of Enrollment:

Liver Center at Saint Michael's Medical Center. 3rd Floor, Bldg. A, 111 Central Avenue, Newark NJ, USA 07102.

In the Liver Center, the main Hepatitis / Infectious Diseases Physician that this study will collaborate with is Dr. Jihad Slim, MD.

Study Patient Population

Treatment-naïve and treatment-experienced genotype 1 and 4 HCV patients with or without compensated cirrhosis will be enrolled in this study.

The inclusion criteria for study are as follows:

1. Male or female 18 years old and above.
2. Be HCV treatment naïve
3. HCV RNA PCR $\geq$ 10,000 IU/L
4. Confirmed infection with Hepatitis C virus (HCV) by HCV serum antibody assay and by HCV Ribonucleic Acid (RNA) Polymerase Chain Reaction (PCR) and Confirmed chronicity with 2 PCR's 6 months apart.
5. Patients with HCV Genotype 1, 4
6. Genotype 1a patients will be required to have historical resistance-associated variants (RAV) testing ot done at screening if not previously performed
7. Patients are candidates for treatment of HCV with oral Direct-Acting Agents (DAA)
8. understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent
9. Abstain from sexual intercourse will taking study medications and for 14 days after the last dose of study medications

Patients will be excluded from the study if they fulfill any of the following criteria:

1. Patient not willing to sign written informed consent
2. Patients deemed not suitable for HCV treatment as deemed by the treating physician at the liver center
3. Patients with decompensated liver cirrhosis, defined as follows:
    a. Liver biopsy within the last year showing Scheuer Stage 4 or transient elastography (Fibroscan®) in the last year with a reading of >12.5 kPa;

AND

b. Any clinical sign of hepatic decompensation such as ascites (fluid in the abdomen), jaundice (yellowing of eyes and skin), esophageal varices with bleeding (enlarged veins of the esophagus seen on endoscopy) or hepatic encephalopathy (tremors, confusion, sleepiness)

4. Co-Infection with the Hepatitis B virus
5. Any liver disease of non-HCV etiology such as Hemochromatosis, Wilson's Disease, Alcoholic liver disease or Non-Alcoholic Steato-Hepatitis (NASH)
6. Hepatocellular carcinoma or any other malignancy
7. Untreated psychiatric conditions such as major depression, schizophrenia, bipolar disorder which in the opinion of the Principal Investigator will not interfere with protocol visit and/or procedures
8. Current and untreated substance abuse (cocaine, opiates, alcohol, marijuana, other recreational drugs, controlled substances)
9. Patient is pregnant or breastfeeding.
10. Patients unwilling to use cellular phones
11. Patients unwilling to follow specific instructions for medication intake
12. Patient has any of the following conditions:
    - Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.
    - Poor venous access that precludes routine peripheral blood sampling required for this trial.
    - History of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).
    - History of a medical/surgical condition that resulted in hospitalization within the 3 months prior to enrollment, other than for minor elective procedures
    - Medical/surgical conditions that may result in a need for hospitalization during the period of the study
    - Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, TNF antagonists, or other immunosuppressant drugs during the course of the trial

13. has exclusionary laboratory values as listed below:

    Noncirrhotic/Cirrhotic Subjects
    Creatinine clearance < 50 mL/min
    Hemoglobin <9.5 g/dL for both male and female subjects
    Platelets <50 x 103/µL
    serum albumin < 3.0 g/dL
    INR >1.7, unless subject has a stable INR on an anticoagulant regimen.
    HbA1c >10%
    ALT >10XULN
    AST >10XULN

14. is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

15. agree to the following:

- The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

- The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice abstinence† from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestinonly pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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Enrollment

Upon signing the informed consent, the following data will be gathered prior to start of treatment: demographic data such as age, gender, race/ethnicity, highest educational attainment, employment status, co-morbid conditions as documented in the patient's records, current medications, vital signs (blood pressure, heart rate, respiratory rate, temperature), CBC with differential count, complete metabolic panel, 12-Lead Electrocardiogram (EKG), Cardiac stress test results if applicable, echocardiogram results if applicable, , BMI, baseline HCV RNA PCR

viral load, HCV genotype, baseline HCV resistance testing (if indicated), results of the Fibroscan® test or liver biopsy.

Once the informed consent is signed and the patient is deemed eligible for treatment, the patient will be randomized to either ARM 1 or ARM 2 in a 1:1 ratio. ARM 1 will be prescribed elbasvirir/grazoprevir with/or without ribavirin for 12 or 16 weeks 1 tablet daily with MEMS Smart Cap with real-time monitoring. Arm 2: elbasvir/grazoprevir with/or without ribavirin for 12 or 16 weeks 1 tablet daily MEMS Smart Cap without real-time monitoring.

For Group 1, the cap of the study drug bottle will be replaced with the Portal724- MEMS Smart Cap. A cellular phone per patient will also be provided. The Smart Cap in this study is to be outfitted to send messages to a website to which only the investigators and the research assistants have access to monitor medication adherence. Patients are to be instructed to open their study drug bottles in areas where there is at least 1 cellular signal bar. Patients will also be instructed to take their medications at specific agreed upon times. Once the agreed upon times are set, these will be programmed into the Smart Caps through a software program. The Smart Caps are encoded to not only record each pill bottle opening, it also will transmit an alert to the aforementioned website when the bottle is not opened within 2 hours of the agreed upon time. This alert is then seen by the Investigator or the Research assistant through a computer or their smartphone. The Investigator or Research Assistant in turn calls the cellular phone provided to the patient to remind the participant to take their medication, thus providing real-time feedback. Group 2 (the control group) will be provided MEMS Smart Cap to record study drug bottle opening, but without real-time feedback and will be managed as per the standard of care at the Liver Center SMMC.

Patients from both groups will be seen in the Liver Center at Day 1, weeks 2, 4, 8 and 12 from start of treatment. They will be seen by Liver Center Physician together with the Investigator and Research Assistant at each visit. They will also be counseled about the importance of medication adherence at every visit by the Liver Center physician. At each visit, patients are instructed to bring with them all of their anti-HCV study drug bottles for pill counting to be done by the Investigator and Research Assistant. Patients in ARM 1 will also get feedback about their medication compliance using the Smart Caps per visit.

After completion of treatment as determined by the Liver Center Physician, patients from both groups are to follow-at week 4 and week 12 post-treatment. At that time, an HCV RNA PCR viral load will be obtained to determine if patient has an undetectable viral load, or Sustained Virologic Response (SVR). SVR is the marker for a functional cure of HCV, or treatment success. Non-SVR would mean treatment failure.

Study Procedures		Pre-Treatment		Treatment Assessments				Post Tx	Post tx
		Screening (Day 35 to -1)	Baseline (Day 0)	WK2	Wk4	Wk8	Wk12/16	Wk 4	Wk 12
Informed Consent w/ Med Hist inc HIV status		x							
Complete PE inc. Vital Signs		x	x						
Symptom Directed PE inc. Vital Signs				x	X	X	X	x	x
12-lead ECG		x							
Chemistry(Comprehensive Metabolic Panel)		x	x	x	x	x	x	x	x
Hematology		x	x	x	x	x	x	x	x
Virology(HCV)		x	x	x	x	x	x	x	x
AEs			X	X	X	X	X	X	X
Con Meds		X	X	X	X	X	X	X	
MEMS download			x	x	x	x	x		

Data Collection

At each visit, the following data are to be collected: HCV RNA PCR viral load, CBC, complete metabolic profile, number of pills missed. For both groups, Number of times pill bottles were opened will also be collected.

Primary outcome measures:

Primary endpoint in the study is the effect of the use of Portal724-MEMS Service on medication adherence, defined as compliance to regimen ≥ 95% of the time.

Secondary outcome measures:

The secondary endpoints for the study include the effect of the use of Portal724-MEMS Service on SVR, factors that affect medication adherence, such as race/ethinicity, age, educational attainment. Additionally, the feasibility of using MEMS adherence technology in an inner city urban population will be evaluated.

Statistical Analysis

This is a pilot study intended to generate initial data on the use of MEMS technology in an inner city population to assess its feasibility and impact on treatment outcomes in HCV infected patients. Wilcoxon signed-rank test will be used to compare Groups 1 and 2 in terms of achieving adherence 95%.

SVR between the groups will also be analyzed in the same manner. A descriptive analysis will be done outlining patients' profiles. Fischer's exact test will be used to compare baseline characteristics between Groups 1 and 2. Alpha level for all statistical analysis will be set at 0.05.

Toxicity management

Grazoprevir/elbasvir

The following side effects have been reported when MK-5172 in doses ranging from 25 mg to 800 mg or placebo (a tablet that looks the same as the MK-5172 but has no active ingredient) was given for up to 12 continuous weeks to 389 HCV-infected men and women at the same time as other drugs commonly given to HCV patients (pegylated interferon and ribavirin). These side effects were considered to be related to the treatment.

- Decrease in the blood cells that carry oxygen
- Decrease in blood cells that fight infection
- Stomach pain
- Diarrhea
- Upset stomach
- Dry mouth
- Nausea
- Vomiting
- Weakness
- Chills
- Fatigue
- Flu-like illness
- General pain
- Fever
- Decreased appetite
- Back pain
- Muscle pain
- Dizziness
- Metallic taste
- Headache
- Trouble falling asleep or staying asleep
- Feeling Irritable
- Cough
- Shortness of breath
- Hair loss
- Dry skin
- Itchiness
- Rash
- Pain in the joints

Most of these side effects were mild to moderate in intensity and short lived. While receiving MK-5172 with pegylated interferon and ribavirin, about half the patients had increases in serum total bilirubin (a substance in your blood that is made in the body that is removed by the liver) and these values decreased in these patients over time while continuing MK-5172. In some patients, blood tests of the liver called 'transaminases' which may be related to liver injury were increased at or after 6 weeks of therapy with MK-5172. In one case a patient was hospitalized. The highest transaminase increases were observed at the two highest MK-5172 doses (400 and 800 mg) given to patients in the study. In most patients the transaminase levels decreased after the dosing was stopped including in the patient who was hospitalized.

In two treatment studies of MK-5172 given with pegylated interferon and ribavirin, three patients who received MK-5172 reported drug-related, serious side effects (a side effect that caused hospitalization) while on MK-5172 therapy. One patient who received the 400 mg dose of MK-

5172 reported severe dehydration. A second patient who received the 800 mg dose of MK-5172 had a high increase in transaminase levels which went back to normal after the drug was stopped. A third patient who received the 200 mg dose of MK-5172 reported severe anemia (a decreased number of red blood cells). In all three cases the patients were treated for the serious side effect which resolved.

Fourteen patients have discontinued the MK-5172 therapy early due to a side effect. In some cases the patients discontinued only MK-5172 and in other cases the patients discontinued all therapy. The side effects that led to the study drug being stopped included decrease in the blood cells that carry oxygen, increased bilirubin, low blood pressure, weakness, headache, flu-like illness, irritability, shortness of breath, dehydration, fear/nightmares, anxiety/depression, increased levels of transaminases, nausea, reactivation of chronic pancreatitis (inflammation of an abdominal gland) and myositis (inflammation of the muscles). Not all of these side effects were considered to be related to MK-5172.

Ribavirin
COMMON ADVERSE EVENTS

The most common side effects when taking ribavirin combined with pegylated interferon are flu-like symptoms consisting of:

- Body aches and pains
- Fever
- Chills
- Headache
- Overall feeling of sickness
- Rash

Other common side effects are: anxiety, mood changes, depression and irritability.

The most serious side effect seen with RBV is anemia (a decrease in the number of red blood cells in your body that carry oxygen). Which may cause tiredness and lack of energy. Other side effects may occur which are not listed here or were not seen before.

Ribavirin can cause severe damage and even death of an unborn child or fetus. **Extreme care should be taken to prevent pregnancy while you are taking RBV and afterwards. Patients will be required to abstain from sexual course while taking ribavirin and for 6 months after the last dose of ribavirin**

DILI

In the event of a discontinuation of grazoprevir/elbasvir for suspected ***DILI***, other clinically significant liver chemistry elevations (defined under “Liver Chemistry Stopping and Follow up Criteria", below), severe skin reaction or hypersensitivity reaction, subjects should not restart grazoprevir/elbasvir due to the risk of a recurrent reaction; such subjects should be withdrawn from study and seek/be reviewed for alternative HCV therapy.

Allergic Reaction

Subjects may continue study medication for Grade I or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade 2/3 allergic reactions that are considered to be possibly or probably related to the study medication should permanently discontinue the regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

Adverse events

Adverse Experience (Event)

An adverse experience means any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with any use of the Merck product whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the product, is also an adverse experience.

Serious Adverse Experience

A serious adverse experience (SAE) is any adverse experience occurring at any dose that:

- Results in death
- Is life threatening (places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred)
- Results in a persistent or significant disability/incapacity
- Results in or prolongs an existing inpatient hospitalization
- Is a congenital anomaly/birth defect
- Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not require hospitalization, or development of drug dependency or drug abuse.
- Is an overdose (whether accidental or intentional)
- Cancer (that is not the condition under the study)*

*If disease progression is noted during a protocol-specified reevaluation of the status of a patient's cancer and the progression is manifested solely by results of tumor markers and/or radiologic imaging, that occurrence of progressive disease will NOT be recorded as an adverse experience.

All Serious Adverse Experiences, regardless of causal relationship to the investigational product, must be forwarded to **Merck Worldwide Product Safety** via fax (**215-993-1220**) within 2 working days of the investigator becoming aware of the event and no later than 3 calendar days.

Minimum protocol required language (ie, site has most of the language noted above):

Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) will be provided with copies of all serious adverse experiences regardless of causality to use of a Merck product within two working days. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported (Attn: Worldwide Product Safety; FAX 215 993-1220).

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators by the investigator. This submission will be cross referenced according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, a copy of these reports will be submitted to Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission

Ethics

Institutional review board

Before initiation of the study, the Investigator(s) will submit the study protocol, sample Informed Consent Form, and any other documents to the IRB for approval. The study will not commence until there is full !RB approval. All IRB regulatory material will be properly filed and available for review by the proper organizations.

Confidentiality

Patients will be assigned research participant numbers which will be used by the investigators to identify them. This number plus other data that will be collected from the participants will be kept in password-protected file, only accessible to the Investigator and Research Assistant. Data transmitted by the Portal724- MEMS Smart Cap will only be identified through the research participant number.

Statistical Analysis

This is a pilot study intended to generate initial data on the use of MEMS technology in an inner city population to assess its feasibility and impact on treatment outcomes in HCV infected patients. Wilcoxon signed-rank test will be used to compare Groups 1 and 2 in terms of achieving adherence ≥ 95%. SVR between the groups will also be analyzed in the same manner. A descriptive analysis will be done outlining patients' profiles. Fischer's exact test will be used to compare baseline characteristics between Groups 1 and 2.

Scientific Data Dissemination

It is the intention of the study investigators to submit abstracts & present results of this pilot study at major scientific congresses such as AASLD (American Association for Study of Liver Diseases) or DDW (Digestive Disease Week). The final results of study will be submitted for publication in a major peer reviewed medical journal in Infectious Diseases or Gastroenterology as deemed appropriate at the end of study.

Significance of Research Outcomes

The findings of this research study will have significant implications on our understanding of patient adherence to treatment and health care outcomes. If the use of MEMS technology proves feasible & useful in this inner city environment based on this pilot trial, the investigators envision embarking on a larger research initiative to fully use the technology in patients with HCV, HIV and other chronic infectious and non-infectious disease conditions.

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