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The first in the world human proof-of-concept study on disinfection and healing acceleration capabilities of 222nm Wave Length Narrow Band Ultraviolet Lighting Device.

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OCTOBER 16, 2016

# CLINICAL TRIAL PROTOCOL

## **PROTOCOL TITLE:**

The first in the world human proof-of-concept study on disinfection and healing acceleration capabilities of 222nm Wave Length Narrow Band Ultraviolet Lighting Device.

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# 1 BACKGROUND AND RATIONALE

## 1.1 General Introduction

Recent outbreaks of Ebola and MERS, and in the trend of growing threat of MRSA and multi-drug resistant pathogens, it is clear that we need a new means of countering the infectious threat – even the US, EU, and Korean hospitals with the latest facilities has failed to stop the spread of these pathogens inside their wards. This novel “Harmless UV Light,” operating within the “Safe Zone Wave Length,” will be a disruptive technology to counter the growing threats of infectious diseases, such as multi-drug-resistant bacteria and also viruses such as Ebola, MERS and new type Influenza. It will be a disruptive device in that it aims to be applied to fast, effective and labor-free disinfection of living environments, such as hospital wards, airports, and other public spaces to stop the spread of pathogens. This research is the first human clinical trial using this device that will spearhead the development of this technology, providing the key starting clinical data which would be the lead to development for a wider range of indications and markets. Successful proof of concept will lead to the next stage collaboration of larger scale clinical trials, and trials targeting wider range of indications and markets, at NUHS. This will bring strong opportunities for joint application to Japan (AMED) and Singapore government grants, and joint marketing strategy to Asia. Pressure sore has been selected as the first target disease because of (1) its large need for effective treatment from increasing prevalence in aging society, (2) its rather uniform pathology based around bacterial infection, and (3) easiness to quantitatively measure the degree of bacterial infection and the rate of healing.

The device to be used in this study is a UV-Photo Disinfection device. Safe zone UV (SUV) irradiation (222 nm) to be used for the study will be manufactured by Ushio Inc. It is currently not in use in humans. UV light is a well-established anti-microbial modality, effective both against bacteria and viruses

## 1.2 Rationale and Justification for the Study

### 1.2.1 Rationale for the Study Purpose

Previous preliminary work by Ushio Inc. and Columbia University (Industry) in 2013, Buonanno et.al, reported that 190nm-230nm UV light is as efficient as conventional germicidal lamps for inactivating MRSA, but is far safer in regard to human exposure. UV light at a wavelength of around 200 nm is very strongly absorbed by proteins, so its ability to penetrate biological material is very limited. For example, the intensity of ~200-nm UV light is reduced by half in only about 0.3  $\mu\text{m}$  of tissue, compared with about 3  $\mu\text{m}$  at 250 nm and much longer distances for higher UV wave-lengths. The very short range in biological material of the ~200-nm far-UVC wavelength means that, while it can penetrate and kill bacteria and viruses, it cannot penetrate the cell nucleus of individual human cells – typical human cells range in diameter from about 10 to 25  $\mu\text{m}$ . Buonanno et al showed the experimental result of inactive MRSA by using 207nm excimer lamp. Testing using 254nm,222nm and 207nm lamps in inactivating MRSA was done. 207nm,222nm UV-C lamp were showed to have the same capability of germicidal UV lamp(254nm) for inactivating bacteria and viruses.

As for in-vitro safety data, there are two studies performed. Mutation of DNA did not happen in both cases of 207 and 222nm irradiation. As for in-vivo safety data, preliminary study was performed in hairless mouse skin. The hairless mice were exposed to monochromatic 207-nm

UV by a filtered KrBr excimer lamp and a standard germicidal lamp UV (254 nm). The mice were sacrificed and dorsal skin sections were analyzed in terms of induction of cyclobutane pyrimidine dimers (CPD), and induction of pyrimidine-pyrimidone 6-4 photoproducts (6-4 PP). The epidermal layer thickness of dorsal skin exposed to 207 nm light was not statistically different from controls, by contrast, that was generated by 254 nm light resulted in a 2.7 fold increase. Exposing to 254 nm light resulted in a dramatic increase versus controls in the percentage of premutagenic skin lesions CPD and 6-4 PP in epidermal cells, whereas the tissue exposed to the same fluence of 207 nm UV light showed no statistically significance increase of these epidermal lesions relative to the controls. Minimal erythema dose test (MED) of healthy volunteer skin was also performed. It was found the 207 nm and 222 nm MED of the skin is much higher than that of 254nm. The 207nm light did not display any sign of erythema up to 50mJ/cm<sup>2</sup>, although the MED of 254nm is 10mJ/cm<sup>2</sup>. For the 222nm, erythema did not occur up to 300mJ/cm<sup>2</sup>.

This study is a first in human proof of concept that the 222nm UV light is as effective in human subjects as compared to the in-vitro studies mentioned above.

## **2 HYPOTHESIS AND OBJECTIVES**

### **2.1 Hypothesis**

UV light is a well-established anti-microbial modality against bacteria and viruses - yet conventional 254nm UV light is associated with raised risks of skin cancers and cataracts that limit its use. A new UV lamp by Ushio Inc. emits selected wave length of 222nm that has demonstrated in previous in vitro and in vivo studies, to cause significantly less harm to human cells, while maintaining major disinfecting capabilities.

### **2.2 Primary Objectives**

This proof-of-concept study aims to demonstrate the efficacy of the “Safe-Zone” 222nm Ultraviolet-C (UVC) light to manage bacterial infection in pressure sore and accelerate healing of pressure sore by removing bacterial infection which is known to play a major role in slowing the healing of these wounds.

### **2.3 Potential Risks and Benefits:**

#### **2.3.1 Potential Risks**

The downside to the more widespread use of UV radiation in these contexts is that in most wavelengths it is a human health hazard, being both carcinogenic and cataract genic

#### **2.3.2 Potential Benefits**

UV light is a well-established anti-microbial modality, effective both against bacteria and viruses. Studies of surgical wound irradiation with conventional germicidal UV lamps have shown great promise, with UV doses corresponding to 4 to 5 logs of MRSA cell kill, resulting in significant decreases in SSI rates, both of which are extremely important to improved pre-surgical skin

disinfection, and to the effective treatment of infected serious wounds, such as infected diabetic ulcers.

### **3 STUDY POPULATION**

#### **3.1 List The Number and Nature of Subjects to be Enrolled.**

20 patients with presence of pressure sore estimate at 2 cm X 2 cm or bigger will be recruited in NUH for a period of 2 years

#### **3.2 Criteria for Recruitment and Recruitment Process**

Criteria for recruitment will be all patients with the presence of pressure sores estimating a size of 2 x 2 cm or bigger. The patient will be recruited during consultation either in the ward or clinic by the PI and study team members

#### **3.3 Inclusion Criteria**

All patients with pressure sore estimate at 2 cm X 2 cm or bigger will be recruited in NUH for a period of 2 years. The lower age limit of recruitment is 21 and the upper age limit of recruitment is 100 years old.

#### **3.4 Exclusion Criteria**

Patient who has pressure sore exposing bone  
Patient who are beyond the age limits  
Patient who is septic  
Patient with obviously infected wound / pus in the wound  
Patient who is pregnant.

#### **3.5 Subject Replacement**

N.A.

### **4 STUDY DESIGN**

20 patients with presence of pressure sore estimate at 2 cm X 2 cm or bigger will be recruited in NUH for a period of 2 years. Using Ushio's prototype, narrow-band 222 nm UV light will be irradiated onto selected pressure sore area for 90 seconds, 2 times per week over 2 weeks duration after the wound is cleaned and dry. A plastic sheet with a hole of 2 cm X 2 cm will be used to guide the UV Light positioning on the pressure sore and to ensure that irradiation is shielded and will be blocked to only target at the selected pressure sore area. The UV light will be held at 1cm above the pressure sore. Wound culture and sensitivity before and immediately after each UV treatment will be done to determine if there is any decrease in bacteria count. Result can be used to determine the presence of wound infections prior to/after the UV treatment. Secondary to that, pictures of the selected pressure sore area before and after UV treatment will be taken and healing rate will be measure using Pictzar program. Healing rate will be estimated by scaling the size, the color, the edge form and the elasticity by using a color camera until the sores heal up to 50% to the full recovering to see if there is any decrease in wound size. After the trial, researchers will suggest improvements to the device from clinical perspective which will lead to mass production types. Successful result will be followed by a

larger scale clinical test at NUHS with joint application to Japan (AMED) and Singapore government grants, and joint marketing strategy to Asia

A more detailed description of the process of sample collection is attached in Appendix 1.

#### **4.1 Randomisation and Blinding**

N.A.

#### **4.2 Contraception and Pregnancy Testing**

Patients who are pregnant will be excluded from this study

#### **4.3 Study Visits and Procedures**

##### **4.3.1 Screening Visits and Procedures**

Using Ushio's prototype, narrow-band 222 nm UV light will be irradiated onto selected pressure sores area for 90 seconds, 2 times per week over 2 week duration after the wound is cleaned and dry.

No additional hospital visits will be required.

Regular wound cleaning / debridement and dressings of the pressure sore will be performed

##### **4.3.2 Study Visits and Procedures**

Using Ushio's prototype, narrow-band 222 nm UV light will be irradiated onto selected pressure sores area for 90 seconds, 2 times per week over 2 week duration after the wound is cleaned and dry.

No additional hospital visits will be required.

Regular wound cleaning / debridement and dressings of the pressure sore will be performed

##### **4.3.3 Final Study Visit:**

Final study visit will be the last day of the 2 week long treatment process

##### **4.3.4 Post Study Follow up and Procedures**

N.A.



## **4.4 Discontinuation/Withdrawal**

### **4.4.1 Discontinuation Criteria**

N.A.

### **4.4.2 Discontinuation Visit and Procedures**

N.A.

## **5 TRIAL MATERIALS**

N.A.

### **5.1 Trial Product (s)**

A prototype UV photo-disinfection device developed by Ushio. It consists of a 222nm light emitting device which is made up of a lamp house and a main body.

### **5.2 Storage and Drug Accountability**

The product will be stored in a room temperature, dry storage area. The product will be tested the day before designated therapy with the trial subjects.

## **6 TREATMENT**

### **6.1 Rationale for Selection of Dose**

N.A.

### **6.2 Study Drug Formulations**

Using Ushio's prototype, narrow-band 222 nm UV light will be irradiated onto selected pressure sores area for 90 seconds, 2 times per week over 2 week duration after the wound is cleaned and 2dry

### **6.3 Study Drug Administration**

Using Ushio's prototype, narrow-band 222 nm UV light will be irradiated onto selected pressure sores area for 90 seconds, 2 times per week over 2 week duration after the wound is cleaned and dry

### **6.4 Specific Restrictions / Requirements**

N.A.

### **6.5 Blinding**

N.A.

## **6.6 Concomitant therapy**

Regular wound debridement and dressing changes will be performed as per regular treatment for pressure sores.

## **7 SAFETY MEASUREMENTS**

### **7.1 Definitions**

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
- is a medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

### **7.2 Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to DSRB**

Reporting of adverse events involves the PI submitting to the approving DSRB the completed SAE Reporting Form within the stipulated timeframe. PI is responsible for informing the institution representative (local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

### **7.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)**

All SAEs that are unexpected and related to the study drug will be reported to HSA. All SAEs will be reported to HSA according to the HSA Guidance for Industry “Safety Reporting Requirements for Clinical Drug Trials.”

The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-up information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

## **8 DATA ANALYSIS**

### **8.1 Data Quality Assurance**

Pictures of the wound before and after UV treatment will be taken and healing rate will be measure using Pictzar program. Healing rate will be estimated by scaling the size, the colors, the edge form and the elasticity by using a camera until the sores heal up to 50% to the full recovering.

Pictures and samples will be taken by the same person to prevent any variance in sampling techniques

The investigators and the collaborators in the study team will be responsible for the safety of the data.

### **8.2 Data Entry and Storage**

The pictures and data will be kept for the duration of the study in the PI password protected Laptop. The study team members will have access to the pictures or data if they need it.

## **9 SAMPLE SIZE AND STATISTICAL METHODS**

### **9.1 Determination of Sample Size**

N.A

### **9.2 Statistical and Analytical Plans**

N.A

## **10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

Study members will be given direct access to data should they need it

## **11 QUALITY CONTROL AND QUALITY ASSURANCE**

The investigators and the collaborators in the study team will be responsible for the safety and accuracy of the data.

The electronically stored data will include minimal necessary information mainly wound sites, sites where culture is taken, time where culture is taken, result of culture test, some demographic data and details of treatment implemented.

It will be reviewed by the PI on a monthly basis. Any significant findings will be recorded as well.

## **12 ETHICAL CONSIDERATIONS**

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

The principle investigator is responsible for informing the DSRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement.

### **12.1 Informed Consent**

After the team has discussed the treatment plan to the potential research participant, they will be given adequate time to consider whether they want to participate in our research study. Consent process will only take place after potential research participant consider that option in either the Outpatient Clinic or Inpatient Ward setting.

The study team who are also the attending team will be taking the consent

Potential research participant will be given adequate time to consider whether they want to participate in our research study before any consent is taken from them

### **12.2 Confidentiality of Data and Patient Records**

The electronically stored data will include minimal necessary information mainly wound sites, sites where culture is taken, time where culture is taken, result of culture test, some demographic data and details of treatment implemented. It will be reviewed by the PI on a monthly basis. No patient identifiers will be taken during the study

## **13 PUBLICATIONS**

N.A.

## **14 RETENTION OF TRIAL DOCUMENTS**

Pictures and data will be deleted after the data has been published

## **15 FUNDING and INSURANCE**

National Clinical Trial Insurance will be responsible for payment and compensation of injury or illness arising from participation of subjects in the study

The study is funded by the GCC grant call.

# **List of Attachments**

**Appendix 1      Wound Sampling procedure**

## Appendix 1

### Procedure to obtain wound swab samples

1	Consent obtained from patient
2	Wound is exposed
3	Bedside wound debridement is performed <ul style="list-style-type: none"><li>- Eschar is excised</li><li>- Slough removed</li></ul>
4	Irrigation of the wound with 0.9% Normal saline to be performed
5	A photo of the wound using the designated study camera to be taken
6	A Tegaderm with the wound dimensions is fashioned and applied over the wound, exposing the wound bed but covering the wound edges
7	A swab of the wound bed is taken. *
8	One time use pre-made 2x2 headframe is put over the UV light device
9	UV light therapy is commenced over the wound bed 1 cm from the wound bed for 90sec at 6mJ/second for a total of 540 mJ <ul style="list-style-type: none"><li>- The device is to be held directly above the wound bed at right angles</li></ul>
10	A swab of the wound bed is taken immediately after UV light therapy *
11	The Tegaderm is removed
12	A photo of the wound using the designated study camera to be taken
13	The wound is dressed with Allevyn dressing

\*Wound swab samples to be taken with sterile wound swab tip.

The samples will be stored in a sterile dry tube and send to the Microbiology Lab at NUH