Clinical Investigational Plan

ivWatch SmartTouch Sensor:

Device Validation for Infiltrated Tissues

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Project Summary

Peripheral intravenous (PIV) therapy is one of the most common invasive procedures performed in US hospitals. PIV failures often occur when fluids leak out of the vein into surrounding tissue. This failure is called an infiltration for the leakage of non-vesicant solutions or an extravasation for vesicant solutions. The ivWatch Model 400 is a device that assists medical professionals in monitoring patients for PIV infiltration and extravasation events using an optical sensor. This device received FDA clearance for use in the adult and pediatric age groups in February 2015 and December 2016, respectively. The corresponding FDA letters are included on Page 51.

ivWatch is enhancing the Model 400 to support a new disposable electronic sensor, called SmartTouch. In this study, the SmartTouch sensor cable will be tested to show equivalence to the original Model 400 fiber optic sensor. The new sensor design includes optical components in the sensor package, similar to a typical pulse oximeter. This design allows the sensor to be lower cost and disposable. The goal of this study is to validate the performance of the ivWatch SmartTouch sensor for detecting the early stages of an IV infiltration, as collected from healthy adult volunteers. The Model 400 Fiber Optic sensor is used for performance comparison.

The study objectives include:

Primary Objective: Demonstrate a statistically significant improvement for detecting early stage infiltrations in comparison to hourly observation by a perfect clinician.

Secondary Objectives:

1. Demonstrate statistical equivalence in infiltration detection volume of the SmartTouch and Fiber Optic sensors.
2. Demonstrate statistical equivalence in infiltration sensitivity of the SmartTouch and Fiber Optic sensors.

General Information

Protocol Title:

ivWatch SmartTouch Sensor: Device Verification for Infiltrated Tissues

Name and Address of Sponsor:

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All investigators work at ivWatch, LLC and have the following address and phone number. The clinical study will take place at this location.

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Rationale and Background

Peripheral intravenous (PIV) therapy is one of the most common invasive procedures performed in US hospitals. Over 25 million patients, or approximately 80% of hospital patients, require intravenous therapy each year in the United States [1]. Despite widespread use, a number of potential complications can occur during PIV therapy. Infiltration is the most common mode of PIV catheter failure, with an average incidence rate of 23.9% according to a prospective randomized review of controlled studies from 1999 to 2014 [2]. The other common modes of failure are catheter occlusion / mechanical failure (18.8%), catheter-related phlebitis (15,4%), catheter dislodgement (6.9%), and catheter-related infection (0.2%) [2]. A multicenter trial indicated infiltrations occurred 27-32 times per 1000 intravenous catheter days in adults [3]. Infiltration is the leakage of non-vesicant fluids like saline into the surrounding tissue. Extravasation is the leakage of vesicant fluids, which include cytotoxic drugs, intravenous nutrition, and calcium, potassium, and bicarbonate solutions [4].

IV infiltration or extravasation is usually accompanied by pain, erythema, and/or edema in the vicinity of the insertion site. Severe infiltration and extravasation may lead to necrosis requiring skin debridement, skin grafting, or amputation [5]. One common area of malpractice lawsuits filed against physicians and nurses involves infiltration or extravasation [6]. It has been reported that the infiltration rate for contrast media injections is independent of infusion rate and it does not vary significantly with regard to injection site, catheter size, or catheter type [7]. A randomized controlled trial including 3,283 adult medical and surgical patients with 5,907 total catheters indicated that PIV catheter occlusion rate (including infiltration) is improved by forearm insertion versus hand, antecubital fossa, or upper arm [8]. The reported incidence of infiltration in the neonatal intensive care unit (NICU) population is between 23% and 78% and carries the potential for long-term sequelae [9].

ivWatch, LLC has developed the ivWatch Model 400 – a Class II medical device that is cleared for use on adults and pediatrics. The ivWatch Model 400 is indicated for the detection of subcutaneous infiltrations and extravasations of 10 cc or less of optically clear infusates, as an adjunctive device to the clinical evaluation in the healthcare setting of adults and pediatrics with PIVs.

The ivWatch Model 400 consists of the ivWatch Patient Monitor (IPM), reusable fiber optic sensor cable, and sensor cable receptacle. As illustrated in Figure 1 below, the reusable fiber optic sensor delivers visible and near-infrared light to the tissue and transmits reflected light back to the IPM. The IPM contains an optical system that generates light signals that are sent to the patient's skin (via the reusable fiber optic sensor cable), and measures the light returning from the patient's skin (also via the reusable fiber optic sensor cable). The sensor head of the reusable fiber optic sensor cable is held in place and attached to the patient using the sensor receptacle. The IPM also contains the hardware for executing the proprietary ivWatch signal processing algorithm, and for displaying system status on a user interface, including audible and visual notifications indicating changes to the state of the PIV.

When changes in the diffuse reflectance in the tissue near the peripheral IV insertion site are consistent with an infusate pooling in the subcutaneous tissue, the IPM emits audible and visual

notifications intended to prompt the clinician to inspect the peripheral IV site for a possible infiltration event. Prompt identification of infiltrations reduces the risk of injury to patients undergoing peripheral IV therapy and improves the likelihood of receiving the correct dosage of medications delivered intravenously.

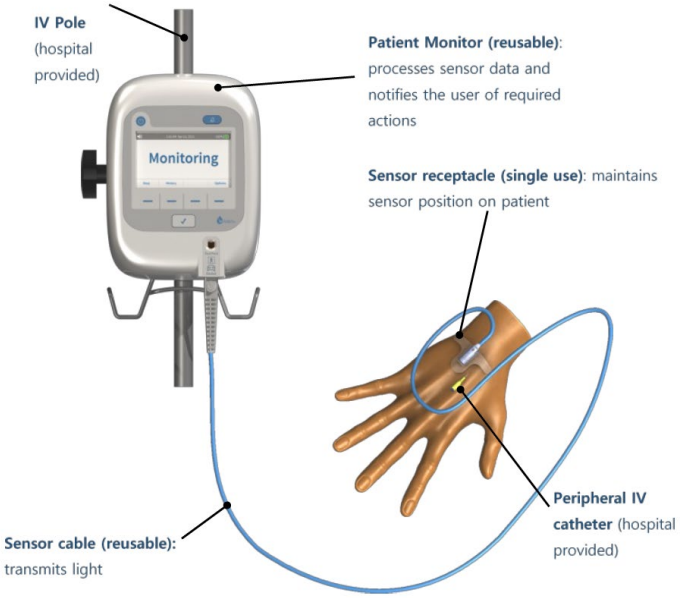


Figure 1. ivWatch Model 400 Infiltration Monitoring System

The ivWatch Model 400 system has been expanded to support both the fiber optic sensor cable configuration of the existing Model 400 as well as an electronic sensor cable configuration (SmartTouch). The SmartTouch sensor consists of low-cost optical components built into the sensor head, like disposable pulse oximeter sensors. This design allows the SmartTouch sensor to be a more cost effective single-use sensor, as opposed to the costlier reusable fiber optic sensor. An extension module compatible with the existing ivWatch Model 400 was developed to support an electronic sensor cable configuration, (Figure 2). The Extension Module is connected to the IPM via USB. The SmartTouch sensor was designed to be an electronic version of the Model 400 fiber optic sensor. The sensor is placed on the skin of a patient near the PIV site, following the protocol as the Model 400, and the same indications for use apply.

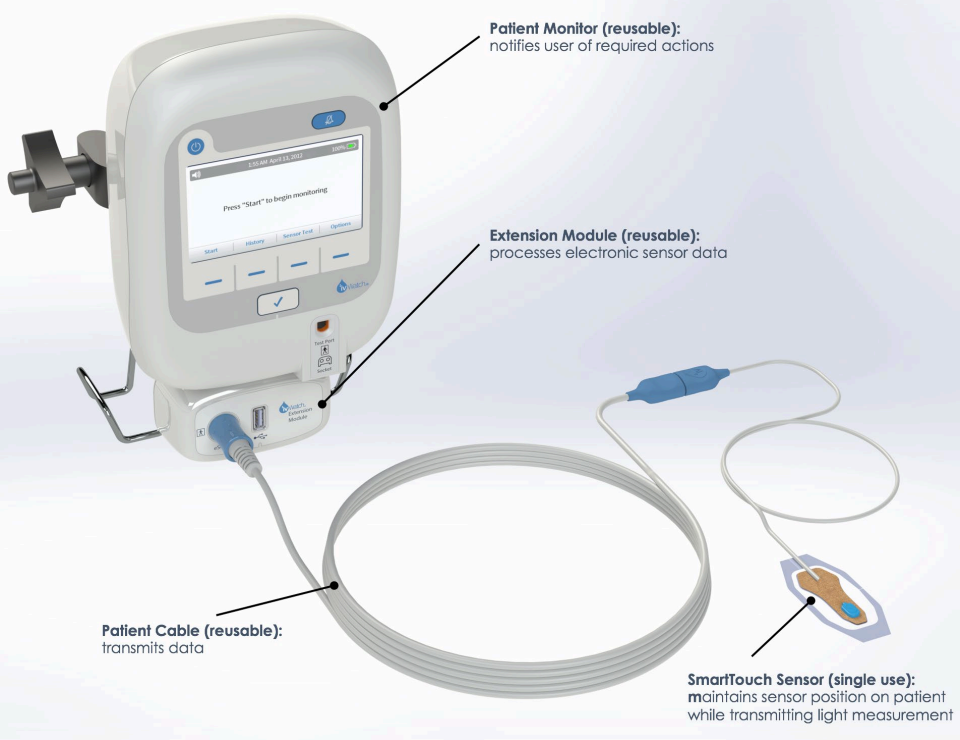


Figure 2. ivWatch Model 400 with Extension Module and SmartTouch Sensor

ivWatch Model 400 Clinical Studies

The ivWatch Model 400 was tested in a series of IRB-approved studies on healthy adult research subjects, as summarized in Table 2. The Design Verification studies evaluated the performance of the device under different conditions. The NIR Detection of PIV Infiltration study evaluated two models of PIV infiltration as well as potential algorithm correction for changes in tissue blood volume. The Signal Variation of Normal Tissue study evaluated the sources and rates of non-infiltration alarms when monitoring normal, non-infiltrated tissues. In this protocol document, the terms 'alarm' and 'notification' are considered interchangeable. Two clinical studies evaluated how the infiltration rate and catheter depth affected the diagnostic performance of the ivWatch Model 400. The device detected all 10mL infiltrations for common adult infusion rates ranging from 5 mL/hr to 150 mL/hr. The device detected all infiltrations with a catheter depth less than 5 mm deep although deeper infiltrations caused a reduced sensitivity by the device. The final study assessed the adhesion of the ivWatch receptacle over a 96 hour period. There were no adhesion issues with the receptacle when used with an occlusive dressing.

After completing the design verification studies, two additional studies were performed to validate the final design. The study, titled Device Validation for Non-Infiltrated Tissues, evaluated non-infiltrated sites over a 24 hour period. The device issued a false red notification once every 4.2 days and a false yellow notification once every 2.0 days. These notifications were often caused by compression of the IV site. The next study, titled Device Validation for Infiltrated Tissues, evaluated the performance of the ivWatch Model 400 for detecting 140 infiltrated IV sites. Of the 140 IV sites, the ivWatch device issued 135 red notifications (96% sensitivity) and 139 yellow notifications (99% sensitivity). These results demonstrated the ivWatch Model 400 is highly sensitive

to infiltrated PIV sites on the hands and forearms of adults while having a false notification rate that should have negligible effects on clinical alarm fatigue.

Three additional IRB-approved studies were performed to (1) examine the infiltration detection performance as a function of the distance separating the catheter tip and ivWatch sensor, (2) examine the infiltration detection performance when the sensor is placed above and below a transparent occlusive dressing, and (3) examine the false notification rate when the sensor is placed above a transparent occlusive dressing.

After the FDA clearance for ages 18 and up, an IRB-approved clinical study was conducted to measure the performance of the ivWatch Model 400 device for detecting early stage infiltrations on pediatric patients at Cincinnati Children's Hospital Medical Center. Hospitalized pediatric patients under the age of 18 who received continuous IV therapy were monitored with the device. The study was broken into two groups, 156 subjects in a blinded non-alarming group, and 57 subjects in an alarming group. The objectives of the study were to determine the amount of time between infiltration detection by the clinician and the device as well as the device sensitivity and specificity. Each site was continuously monitored during IV therapy and the IV was terminated if an infiltration was detected or other complications were identified. In the nonalarming group, the device issued red "Check IV" notifications a median time of 15.2 hours before clinician detection. The device issued notifications for 18 out of 23 clinician-confirmed infiltrations in the non-alarming group, for a sensitivity of 78.3%. In the alarming group, the device issued notifications for 12 out of 15 clinician-confirmed infiltrations. The results from this study were used to support the FDA clearance for all age groups including pediatrics in December of 2016.

ivWatch SmartTouch Sensor Clinical Study Plan

A series of new clinical studies are taking place to test feasibility as well as to verify and validate the SmartTouch sensor in a similar way to the Model 400. Two feasibility studies were completed to examine the 'alpha' design of the SmartTouch sensor in terms of (1) infiltration signal performance and (2) false notification rate of the SmartTouch sensor (Table 3). These studies have indicated the optical design of the alpha SmartTouch sensor performs equivalently to the Model 400 fiber optic sensor. Four verification studies were performed to test the 'beta' SmartTouch design and show equivalence to the Model 400 in terms of (1) device sensitivity and (2) false notification rate. The beta SmartTouch design contains the same optical sensor as alpha, but improvements were made to the sensor for increased durability and manufacturability. Signal data from these verification studies may be used to improve signal processing algorithms prior to final software design.

This clinical protocol is the validation study that will examine the infiltration sensitivity performance of the ivWatch SmartTouch sensor versus the Model 400 fiber optic sensor. This study is modeled after the clinical protocol used to validate the Model 400 system, Device Validation for Infiltrated Tissues (Table 2). The primary objective of the study is to demonstrate a statistically significant improvement for detecting early stage infiltrations in comparison to hourly observation by a perfect clinician, the current clinical standard. The secondary objectives are to demonstrate statistical equivalence in (1) infiltration detection volume and (2) infiltration sensitivity of the SmartTouch and Fiber Optic sensors.

Infiltration Detection by the Perfect Clinician

To be an effective product, the ivWatch sensors must detect early stage infiltrations significantly better than the current nursing standard of care. To facilitate this comparison and provide conservative estimates of the device performance, the idea of a perfect clinician is used, that is, a clinician who assesses the IV site hourly and perfectly classifies the IV site as normal or infiltrated, regardless of how much fluid has been infiltrated into the tissue.

The primary metric used to compare the performance of the ivWatch device with the perfect clinician is the early infiltration sensitivity. The **infiltration sensitivity** is the percentage of early stage infiltrations (<10mL) detected by the ivWatch device or the perfect clinician. For the ivWatch device, the infiltration sensitivity is the ratio of the sites that generate a red alarm to the total number of monitored sites. For the perfect clinician, the infiltration has the same probability of occurring at any time between clinical assessments. Consequently, the percentage of infiltrations detected by the perfect clinician prior to 10mL of infiltrated volume is given by

$$S_C = \min(100\%, \frac{V_{lim}}{R \cdot T_C} * 100\%)$$

where V_{lim} (mL) is the 10mL volume limit, R (mL/hr) is the infiltration rate, and T_C is the observation period (hr). For example, at 100 mL/hr (R=100), the perfect clinician making hourly assessments (T_C=1) of the site would be expected to detect 10% (Clinician Sensitivity = S_C) of the infiltrations prior to 10mL (V_{lim}=10).

Figure 3 illustrates the infiltration sensitivity of a perfect clinician for different infiltration rates and observation periods. A highlighted box indicates common adult infusion rates. The performance of the perfect clinician is limited by how frequently the site can be assessed. If the perfect clinician could monitor the site continuously (observation period = 0), the clinician's infiltration sensitivity would be perfect.

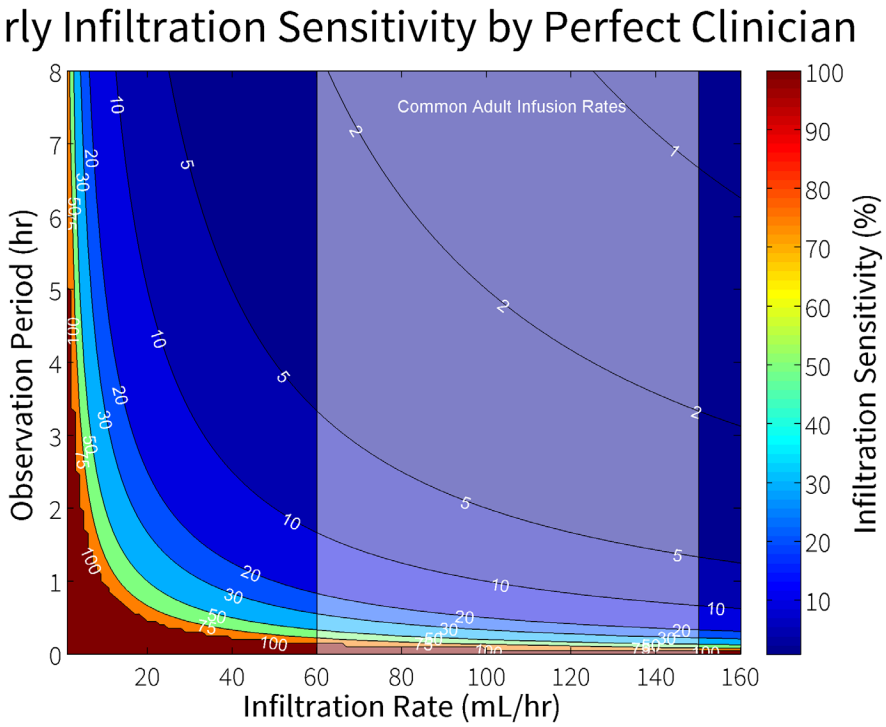


Figure 3. The sensitivity of a perfect clinician for identifying early infiltrations (infiltrated volume < 10mL).

The frequency of IV site assessments can vary significantly in practice depending on the clinician's workload and the perceived risks to the patient. Table 1 includes the assessment frequency recommended in a position paper published by the Infusion Nurses Society [10]. Discussions with clinicians suggest most peripheral IV sites are checked either once per hour or less frequently. As described later, the primary statistical objective in this validation study was performed assuming hourly observation by a perfect clinician.

Table 1. The recommended site assessment frequency by the Infusion Nurses Society.

Assessment Frequency	Description
At least every 4 hours	• Patients who are receiving nonirritant/nonvesicant infusions and who are alert and oriented and who are able to notify the nurse of any signs of problems such as pain, swelling, or redness at the site.
At least every 1 to 2 hours	• Critically ill patients • Adult patients who have cognitive/sensory deficits or who are receiving sedative-type medications and are unable to notify the nurse of any symptoms • Catheters placed in a high-risk location (e.g., external jugular, area of flexion)
At least every hour	• Neonatal patients • Pediatric patients
More frequently (every 5 to 10 minutes)	• Patients receiving intermittent infusions of vesicants

Table 2. Clinical studies performed with the ivWatch Model 400 device.

Study	Purpose	Outcome	Key Performance Metrics
NIR Detection of PIV Infiltration *ivWatch Study ID:* IVWRSCS-01 *Chesapeake IRB ID:* 00008513 *Number of Subjects:* 24 *Number of Sites:* 48 *Dates:* June-August 2013	1. Investigate *in vivo* model of subcutaneous injections near vascular bundles as substitute to through vein infiltrations. 2. Validate sensor and receptacle designs. 3. Investigate and validate effect of tissue blood volume changes on signal.	• Subcutaneous injections are more challenging to detect. • Validated the sensor and receptacle designs. • Insensitive to changes in the tissue blood volume.	**Diagnostic Performance** (all, subcutaneous, through-vein): • Sensitivity: 90%, 83%, 96% • Specificity: 100%, 100%, 100% **Detected Volume** • Through-Vein: 2.0mL • Subcutaneous: 3.3mL
The Signal Variation of Normal Tissue *ivWatch Study ID:* IVW400CS-01 *Chesapeake IRB ID:* 00008218 *Number of Subjects:* 30 *Number of Sites:* 30 *Dates:* August-November 2013	1. Identify sources of non-infiltration alarms. 2. Estimate rates of non-infiltration alarms for patients in an environment that mimics a hospital room. 3. Investigate potential interference between other near infrared devices.	• Negligible impact on clinical alarm fatigue. • Non-infiltration alarms generated by tissue deformation. • No infiltration alarms due to device interference.	**Red Alarm Rate:** • 0.11 red alarms / day • 3 alarms in 661 hours **Yellow Alarm Rate:** • 0.40 yellow alarms / day • 11 alarms in 661 hours
The Effect of Catheter Depth *ivWatch Study ID:* IVW400CS-02 *Chesapeake IRB ID:* 00008254 *Number of Subjects:* 28 *Number of Sites:* 56 *Dates:* September-October 2013	1. Determine relationship between infiltration depth and ivWatch sensitivity. 2. Investigate tissue characteristics that affect ivWatch performance.	• Validation of optical modeling. • ivWatch sensitivity greatest for infiltration depths < 5mm. • Presence of a fascia interposed between catheter tip and sensor reduces sensitivity.	**Depths Less than 5mm (On-Design)** • *1-3mm Deep*: 100% sensitive (12/12) • *3-5mm Deep:* 100% sensitive (17/17) **Depths Greater than 5mm (Off-Design):** • *5-7mm Deep:* 38% sensitive (5/13) • *7-9mm Deep:* 50% sensitive (7/14)
The Effect of Infiltration Rate *ivWatch Study ID:* IVW400CS-03 *Chesapeake IRB ID:* 00008941 *Number of Subjects:* 24 *Number of Sites:* 48 *Dates:* October-November 2013	1. Determine volumes of infiltration fluid required to generate alarm as a function of infiltration flow rate. 2. Determine times required to generate an alarm as a function of infiltration flow rate.	• Detected all infiltrations regardless of infiltration rate. • The response time of the system strongly determines the detected volume when the device alarms.	**Sensitivity & Median Detected Volume** • *5mL/hr:* 100% (12/12) and 0.9mL • *50mL/hr:* 100% (12/12) and 2.2mL • *100mL/hr:* 100% (12/12) and 3.7mL • *150mL/hr:* 100% (12/12) and 5.7mL

Long Term Adhesion of the ivWatch Receptacle *ivWatch Study ID:* IVW400CS-04 *Chesapeake IRB ID:* 00008891 *Number of Subjects:* 6 *Number of Sites:* 18 *Dates:* October 2013	1. Evaluate ability of receptacle to remain adhered to skin over 96-hour period. 2. Evaluate skin integrity after receptacle was adhered for 96 hours. 3. Identify activities that may degrade adhesion of receptacle to the skin.	• ivWatch receptacles remained adhered to skin for 96 hours when combined with occlusive dressing. • The ivWatch receptacle did not cause significant disruption to skin integrity after 96 hours.	**Average Adhesion Time** • *Receptacle Only:* 68 hrs (6 sites) • *Receptacle & Dressing:* 96 hrs (6 sites) • *Receptacle, Dressing, Sensor:* 96 hrs (6 sites)
Device Validation for Non-Infiltrated Tissues *ivWatch Study ID:* IVW400CS-05 *Chesapeake IRB ID:* 00009175 *Number of Subjects:* 40 *Number of Sites:* 40 *Dates:* January 2014	1. Validation trial measuring safety and efficacy of final Model 400 device when monitoring non-infiltrated tissues. 2. Estimate rates of non-infiltration alarms for active patients in a hospital room environment. 3. Demonstrate performance in the presence of interference sources.	• Device can monitor normal tissue with minimal impact on clinical alarm fatigue. • The device can be used without skin irritation or disruption to the skin integrity. • The device operates properly in cases of interference by other light sources.	**Red Alarm Rate:** • 0.24 red alarms / day • 1 red alarm every 4.2 days • 9 alarms in 900 hours **Yellow-Only Alarm Rate:** • 0.51 yellow alarms / day • 1 yellow alarm every 2.0 days 19 alarms in 900 hours
Device Validation for Infiltrated Tissues *ivWatch Study ID:* IVW400CS-06 *Chesapeake IRB ID:* 00009285 *Number of Subjects:* 70 *Number of Sites:* 140 *Dates:* February 2014	1. Validation trial measuring safety and efficacy of final Model 400 device when monitoring infiltrated tissues. 2. Estimate sensitivities of device for detecting early-stage infiltrations (< 10mL infiltrated fluid). 3. Demonstrate significant improvement compared to routine observation by a perfect clinician.	• Detected vast majority of infiltrations regardless of infiltration rate, PIV location, skin pigmentation, or body type. • Significant improvement compared to the current standard – routine observation by a nurse. • No safety concerns were observed – no skin irritation or disruption to skin integrity	**Red Alarm Sensitivity:** • 96.4% Sensitivity • Red Alarm on 135 out of 140 cases • 91.4 to 98.7% for 95% Conf. Interval **Yellow Alarm Sensitivity:** • 99.3% Sensitivity • Yellow Alarm on 139 out of 140 cases 95.5 to 99.96% for 95% Conf. Interval
The Effect of Sensor-to-Catheter Distance *ivWatch Study ID:* IVW-CLR-CS12-400 *Chesapeake IRB ID*: 00010217 *Number of Subjects:* 23 *Number of Sites:* 46 *Dates*: November 2014	1. Quantify the sensitivity of the ivWatch device for each catheter-to-sensor distance. 2. Estimate the detected volume for the yellow and red notifications of the ivWatch device as a function of catheter-to-sensor distance.	• The device detected most infiltrations although the detected volume increased for larger sensor-to-catheter separations • The device sensitivity decreases with larger separations consistent with the hypothesis that the infiltration does not always diffuse uniformly.	**Sensitivity:** • 100% for 10 & 20mm separations • 90% for 30mm separation • 89% for 40mm separation • 78% for 50mm separation **Detected Volume (Median):** • 2.8, 7.7, 12.3, 21.7, 32.8 mL for 10, 20, 30, 40, 50mm separations, respectively.

Infiltration Detection when Placing Over the Dressing *ivWatch Study ID:* IVW-CLR-CS15-400 *Chesapeake IRB ID*: 00013715 *Number of Subjects:* 24 *Number of Sites:* 48 *Dates*: October 2015	1. Estimate the difference in detected volume when placing above and below dressing. 2. Demonstrate statistically significant improvement for detecting early stage infiltrations in comparison to hourly observations by a perfect clinician.	• The device detected most infiltrations with no statistically significant difference in sensitivities for over or under the dressing. • No statistically significant difference between detected volumes for over or under the dressing.	**Sensitivity:** • 100% (24/24) for under the dressing • 95.8% (23/24) for over the dressing **Detected Volume (Mean):** • 2.93 and 2.75 mL for under and over the dressing, respectively.
Performance for Non-Infiltrated Tissues when Placing Over Transparent Occlusive Dressing *ivWatch Study ID:* IVW-CLR-CS16-400 *Chesapeake IRB ID*: 00015068 *Number of Subjects:* 25 *Number of Sites:* 25 *Dates*: April-June 2016	1. Estimate the non-infiltration red and yellow notification rates for the ivWatch device. 2. Determine whether the over-the-dressing red notification rate is significantly less than 1 false red notification per day.	• Red and yellow notification rates occur less than once per day • Device can monitor normal tissue while placed over a clear occlusive dressing with minimal impact on clinical alarm fatigue • Slightly higher notification rates than previous motion studies	**Red Alarm Rate:** • 0.44 red alarms / day • 1 red alarm every 2.28 days • 10 alarms in 548 hours **Yellow-Only Alarm Rate:** • 0.57 yellow alarms / day • 1 yellow alarm every 1.76 days • 13 alarms in 548 hours
Optical Detection of Intravenous Infiltration: A Pilot Study *ivWatch Study ID:* IVW400CS-09 *CCCHMC IRB ID*: 2015-0896 *Number of Subjects:* 243 *Dates*: August 2015 to July 2016	1. Clinical trial in a children's hospital to demonstrate safety and efficacy in pediatric subjects. 2. Time to detection – estimate difference in time when infiltration is detected by clinician and ivWatch. 3. Device sensitivity – estimate ivWatch sensitivity at identifying infiltrations before the clinician. 4. Notification Rate – estimate of the number of notifications per day without clinician-confirmed infiltrations.	• The device detected and alerted clinicians of infiltrations several hours before they are normally found by clinician assessment • The device performance did not depend on the age / size of the subject	**Time to detection:** • Median time difference: 15.2 hours • Range: 1.3 to 99.8 hours **Sensitivity** • 78.3% (18/23) for Non-alarming group • 80.0% (12/15) for Alarming group **Notification Rate** • 0.28 red alarms / day • 0.27 yellow alarms / day

Table 3. Clinical studies performed with SmartTouch sensor.

Study	Purpose	Outcome	Key Performance Metrics
Monitoring Infiltrated Tissues *ivWatch Study ID:* IVW-CLR-CS19-400 *Chesapeake IRB ID:* 00023277 *Number of Subjects:* 64 *Number of Sites:* 128 *Dates:* November 2018	1. Determine if infiltration signals measured with the SmartTouch sensor are equivalent to those measured with the Model 400 sensor. 2. Contribute study data to a database of ivWatch signals of infiltrated tissue. 3. Evaluate processing algorithms to optimize performance of the ivWatch infiltration detection algorithm.	• No statistical difference in the performance of the SmartTouch sensor versus the Model 400 fiber optic sensor, when accounting for catheter depth and distance using a linear regression model. • Catheter depth and distance were significantly different than IVW-CLR-CS06-400, impacting sensitivity but not detection volume.	**Red Alarm Sensitivity** • 91.4% Sensitivity • Red Alarm in 117 out of 128 cases **Yellow Alarm Sensitivity** • 93.0% Sensitivity • Yellow Alarm in 119 out of 128 cases **Detected Volume (mean)** • Red Alarm: 3.7mL • Yellow Alarm: 3.3mL
Signal Variation of Normal Tissue *ivWatch Study ID:* IVW-CLR-CS20-400CS *Chesapeake IRB ID:* 00023891 *Number of Subjects:* 30 *Number of Sites:* 30 *Dates:* December-January 2018	1. Quantify the signal variation of normal tissue in a setting that approximates the hospital room environment. This includes calculating distribution metrics such as mean and standard deviation for the collected signals. 2. Evaluate processing algorithms to optimize performance of the ivWatch device with SmartTouch sensor. 3. Determine if non-infiltration red-notification and yellow-notification rates are equivalent to those recorded with the Model 400 sensor.	• The SmartTouch sensor has a similar false-notification performance to the Model 400 fiber optic sensor. • Both red and yellow estimated notification rates are within the 95% confidence intervals reported in "ivWatch Model 400: Device Validation for Non-Infiltrated Tissues".	**Red Alarm Rate:** • 0.312 red alarms / day • 95% confidence interval 0.133 to 0.733 red alarms / day **Yellow Alarm Rate:** • 0.486 red alarms / day • 95% confidence interval: 0.176 to 1.139 yellow alarms / day

Device Verification for Infiltrated Tissues *ivWatch Study ID:* IVW-CLR-CS22-400 *Chesapeake IRB ID:* 00030567 *Number of Subjects:* 128 *Number of Sites:* 256 *Dates:* December 2018	1. Determine if infiltration sensitivity measured with the SmartTouch sensor is equivalent to the Model 400 fiber optic sensor. 2. Contribute study data to a database of ivWatch signals of infiltrated tissue. 3. Evaluate processing algorithms to optimize performance of the ivWatch device with SmartTouch sensor.	Subject enrollment is complete. The data analysis is in progress.	Analysis in progress
Device Verification for Non-Infiltrated Tissues *ivWatch Study ID:* IVW-CLR-CS23-400 *Chesapeake IRB ID:* 00030569 *Number of Subjects:* 30 *Number of Sites:* 60 *Dates:* December 2018 – January 2019	1. Quantify the non-infiltration red-alarm and yellow-alarm rates for the SmartTouch sensor. 2. Determine if non-infiltration red-notification and yellow-notification rates of the SmartTouch sensor are equivalent to the Model 400 fiber optic sensor. 3. Evaluate signal processing algorithms to optimize performance of the ivWatch device with SmartTouch sensor.	Subject enrollment is complete. The data analysis is in progress.	Analysis in progress
Device Verification for Non-Infiltrated Tissues, Part II *ivWatch Study ID: IVW-CLR-CS26-400* *Chesapeake IRB ID: 00032326* *Number of Subjects: 15* *Number of Sites: 30* *Dates: February – March 2019*	1. Quantify the non-infiltration red-notification and yellow-notification rates for the SmartTouch sensor. 2. Evaluate processing algorithms to optimize performance of the ivWatch device with the SmartTouch sensor. 3. Determine if non-infiltration red-notification and yellow-notification rates are equivalent to those recorded with the Model 400 sensor.	Enrollment is open, 11/15 accepted case studies complete to date.	Analysis in progress

The Effect of PIV Depth and Site *ivWatch Study ID: IVW-CLR-CS25-400* *Chesapeake IRB ID: 00032269* *Number of Subjects: 64* *Number of Sites: 128* *Dates: March 2019*	1. Determine whether the catheter depth has a significant effect on the measured infiltration signal. 2. Determine whether the catheter site has a significant effect on the measured infiltration signal. 3. Contribute study data to a database of ivWatch signals of infiltrated tissue. 4. Evaluate processing algorithms to optimize performance of future ivWatch devices.	Subject enrollment is finished for this study. The data analysis is in progress.	Analysis in progress

Study Goals and Objectives

The goal of this study is to validate the performance of the ivWatch SmartTouch sensor for detecting the early stages of an IV infiltration, as collected from healthy adult volunteers. The Model 400 Fiber Optic sensor is used for performance comparison. The study objectives include:

Primary Objective: Demonstrate a statistically significant improvement for detecting early stage infiltrations in comparison to hourly observation by a perfect clinician.

Secondary Objectives:

1. Demonstrate statistical equivalence in infiltration detection volume of the SmartTouch and Fiber Optic sensors.
2. Demonstrate statistical equivalence in infiltration sensitivity of the SmartTouch and Fiber Optic sensors.

Study Design

Approximately 115 subjects may be enrolled in the study with the goal of achieving 98 accepted case studies. The study coordinator will attempt to enroll at least 20 subjects (20%) with dark skin pigmentation and at least 20 subjects (20%) who are classified as obese by their body mass index (BMI), but these are not required enrollment criteria as skin pigmentation and BMI have proven to be insignificant variables in previous ivWatch studies. The intent is to include subjects with different skin pigmentations and body types such that the study represents the intended population of the device. The duration of each study depends on the randomly selected infiltration rates. A study may take up to 2 hours to complete. This corresponds to the subjects receiving the 5mL/hr infiltration rate.

Medical professionals will be used for the health screening of the subject and placement of the catheters. If the research subject is deemed acceptable for the study, various metrics of each subject will be measured, as summarized in Figure 4. These measurements include the weight, height, blood pressure, forearm circumference, skin tone (light, medium, or dark), and skin classification. The skin classification is performed by using the subject pigmentation worksheet to determine the subject's Fitzpatrick skin type. The subject's body mass index is calculated from the weight and height measurements and is used as a measure of the subject's body type (underweight, normal, overweight, obese). These metrics are recorded for post-study analysis to identify correlations between the measured signal and anatomical/physiological characteristics of the research subjects.

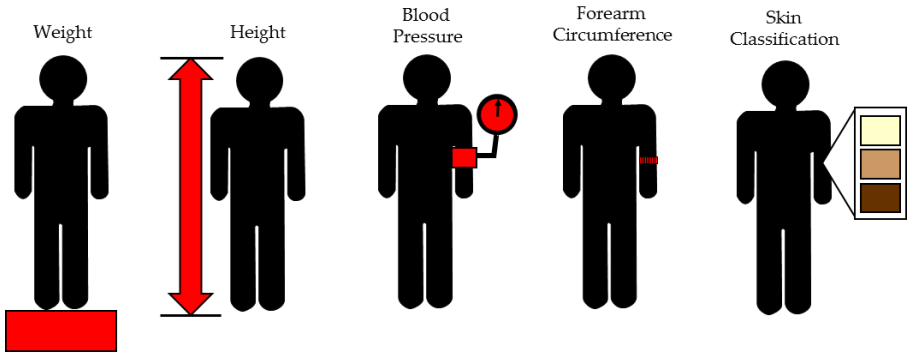


Figure 4. Pre-study measurements performed on each subject.

After completing the informed consent and health history forms, the subject is taken to the test room, which is designed to approximate an infusion center. The room also includes two IV pumps and two ivWatch patient monitors per subject. The study configurations have been randomized and are included in Table 4.

During the study, each subject will receive two subcutaneous injections of isotonic saline solution. These injections will be randomly selected from the four possible locations shown in Figure 5. These four locations represent the most common injection sites for PIV therapy. The subcutaneous injections closely approximate the conditions of a PIV infiltration without exposing the research subject to additional risks and discomforts associated with puncturing a vein (e.g. ecchymosis, hematoma, phlebitis, thrombosis, embolism). The subcutaneous injections will be performed using the same equipment as a PIV procedure.

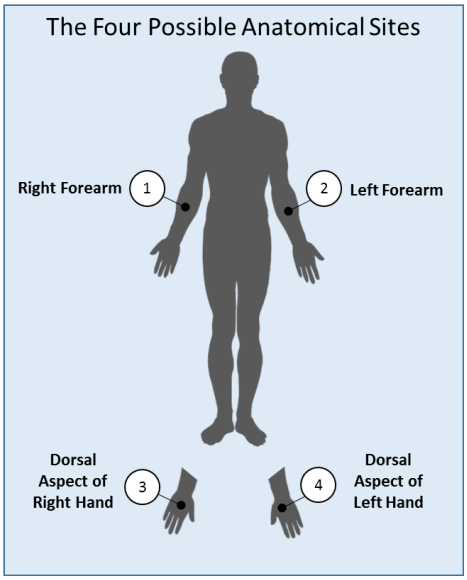


Figure 5. The four possible anatomical sites monitored during this study.

Table 4. The study configuration.

CRF	Site	Rate	Fiber Optic Side	SmartTouch Side	CRF	Site	Rate	Fiber Optic Side	SmartTouch Side
1	Forearm	50	Left	Right	**50**	Forearm	25	Left	Right
2	Hand	5	Right	Left	**51**	Hand	25	Right	Left
3	Forearm	5	Left	Right	**52**	Hand	50	Left	Right
4	Forearm	100	Left	Right	**53**	Hand	75	Right	Left
5	Hand	75	Left	Right	**54**	Forearm	125	Left	Right
6	Forearm	150	Left	Right	**55**	Hand	100	Left	Right
7	Hand	125	Left	Right	**56**	Forearm	75	Left	Right
8	Hand	150	Right	Left	**57**	Hand	75	Left	Right
9	Hand	100	Right	Left	**58**	Hand	5	Right	Left
10	Forearm	100	Right	Left	**59**	Forearm	150	Left	Right
11	Hand	50	Right	Left	**60**	Forearm	25	Right	Left
12	Forearm	150	Right	Left	**61**	Forearm	75	Right	Left
13	Forearm	50	Right	Left	**62**	Hand	150	Right	Left
14	Hand	100	Left	Right	**63**	Hand	75	Right	Left
15	Hand	100	Right	Left	**64**	Forearm	100	Left	Right
16	Hand	5	Left	Right	**65**	Hand	100	Right	Left
17	Forearm	5	Right	Left	**66**	Hand	125	Left	Right
18	Forearm	100	Left	Right	**67**	Hand	25	Left	Right
19	Hand	5	Right	Left	**68**	Forearm	25	Left	Right
20	Forearm	5	Left	Right	**69**	Forearm	5	Left	Right
21	Forearm	125	Right	Left	**70**	Forearm	100	Right	Left
22	Hand	50	Left	Right	**71**	Forearm	50	Left	Right
23	Forearm	50	Left	Right	**72**	Hand	50	Right	Left
24	Hand	150	Left	Right	**73**	Hand	100	Left	Right
25	Hand	125	Right	Left	**74**	Forearm	75	Left	Right
26	Forearm	125	Left	Right	**75**	Forearm	50	Right	Left
27	Forearm	75	Right	Left	**76**	Hand	50	Left	Right
28	Forearm	150	Left	Right	**77**	Forearm	150	Right	Left
29	Hand	125	Left	Right	**78**	Forearm	50	Left	Right
30	Forearm	25	Right	Left	**79**	Hand	150	Left	Right
31	Hand	75	Right	Left	**80**	Forearm	150	Left	Right
32	Hand	25	Left	Right	**81**	Forearm	125	Right	Left
33	Forearm	25	Left	Right	**82**	Hand	75	Left	Right
34	Forearm	125	Right	Left	**83**	Hand	5	Left	Right
35	Hand	50	Right	Left	**84**	Forearm	5	Right	Left
36	Hand	5	Left	Right	**85**	Hand	25	Right	Left
37	Hand	125	Right	Left	**86**	Hand	5	Right	Left
38	Forearm	5	Right	Left	**87**	Hand	50	Right	Left
39	Forearm	50	Right	Left	**88**	Hand	125	Right	Left
40	Hand	150	Right	Left	**89**	Hand	150	Right	Left
41	Forearm	100	Right	Left	**90**	Hand	25	Left	Right
42	Forearm	150	Right	Left	**91**	Forearm	75	Right	Left
43	Hand	25	Right	Left	**92**	Forearm	125	Left	Right
44	Forearm	25	Right	Left	**93**	Forearm	100	Left	Right
45	Forearm	75	Left	Right	**94**	Hand	125	Left	Right
46	Hand	25	Left	Right	**95**	Forearm	5	Left	Right
47	Hand	75	Left	Right	**96**	Hand	100	Right	Left
48	Hand	150	Left	Right	**97**	Forearm	125	Right	Left
49	Forearm	75	Right	Left	**98**	Forearm	25	Right	Left

All subcutaneous injections in this research protocol are infiltrated between 5mL/hr and 150mL/hr, as listed in Table 4. Each injection is limited to a total of 10 mL of saline solution to minimize subject discomfort. This 10mL volume limit corresponds to a 2 hour infiltration at the 5mL/hr IV pump rate and a 4 minute infiltration at the 150mL/hr IV pump rate.

The nurse will examine each site before placing the IV catheters. Photographs of the illumination by a NIR vein viewer will be captured as a record of the subject's vascular structure at the site. The nurse will place the IV catheters at approximately the same anatomical location on each arm. The catheter depth will be monitored and recorded using the SonoSite S-Series ultrasound imaging system, shown in Figure 6. The nurse places the catheter immediately adjacent to a vein typically used for IV therapy. Placing the catheter tip close to the vein wall ensures the saline diffuses similar to a real-world infiltration.

Figure 6. The Sonosite S-Series commercial ultrasound imaging system.

After placement of the catheter, each subject will receive the SmartTouch sensor on one side and the Model 400 fiber optic sensor on the other side according to the random study configuration. The sensor is placed next to the injection site. An example of the ivWatch SmartTouch sensor is shown in Figure 7. The nurse will dress the site using standard hospital procedures and occlusive dressings. Photographs will be captured to record the position of the sensor with respect to the catheter. The sensor cable will be taped to the IV tubing and routed to the IV pole. The IV tubing / ivWatch sensor cable bundle will be secured to the subject using medical tape following standard hospital procedures.

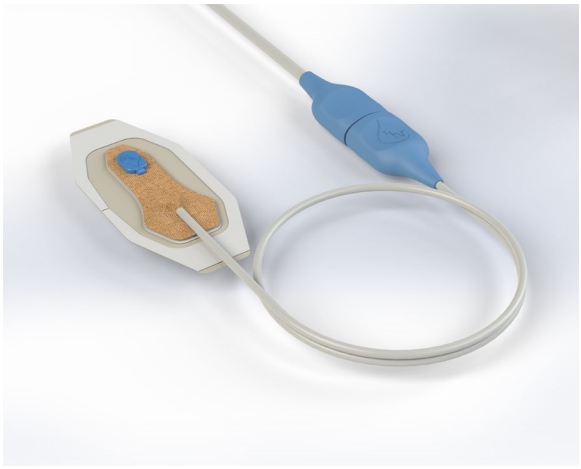


Figure 7. Example of the ivWatch SmartTouch sensor

The sensor is connected to the IPM. A rendering of the patient monitor is included in Figure 8. The rendering identifies the user interface elements on the front face of the IPM. The IPM is attached to the IV pole. The IPM records data during the study and is attached to the IV pole.

Once the ivWatch sensors have been placed on the subject, data acquisition will be started on the two ivWatch patient monitors. This represents time zero (t = 0) in the study. Study staff will record the timing of study events (starting and stopping IPMs, starting and stopping pumps) using a digital wall clock. The pumps will be turned on after 5 minutes of monitoring. The IV pumps will stop after 10mL of isotonic saline solution has been injected into the tissue. Once the pumps have been stopped for both sites, the IPMs will collect data for an additional 5 minutes.

Once the data acquisition is complete, the research assistant captures photographs of the two sites to record the visual appearance of the region. The ivWatch components are removed from the sites. An ultrasound technician will then capture ultrasound images of the sites to record structure of the infiltrated tissue under the sensor and measure catheter depth. The IV's are then removed from the research subject. A final photograph is captured of the bare sites. The photographs are intended to record the skin integrity, such as whether the research subject had an allergic reaction to any materials or if the skin was damaged when removing adhesive-backed sensors.

ivWatch, LLC believes this study design provides the signal characteristics that are representative of those expected in a clinical setting. This data will enable the researchers to understand differences, if any, between the optical signal characteristics of infiltrated tissue data collected with the SmartTouch sensor versus the Model 400 sensor.

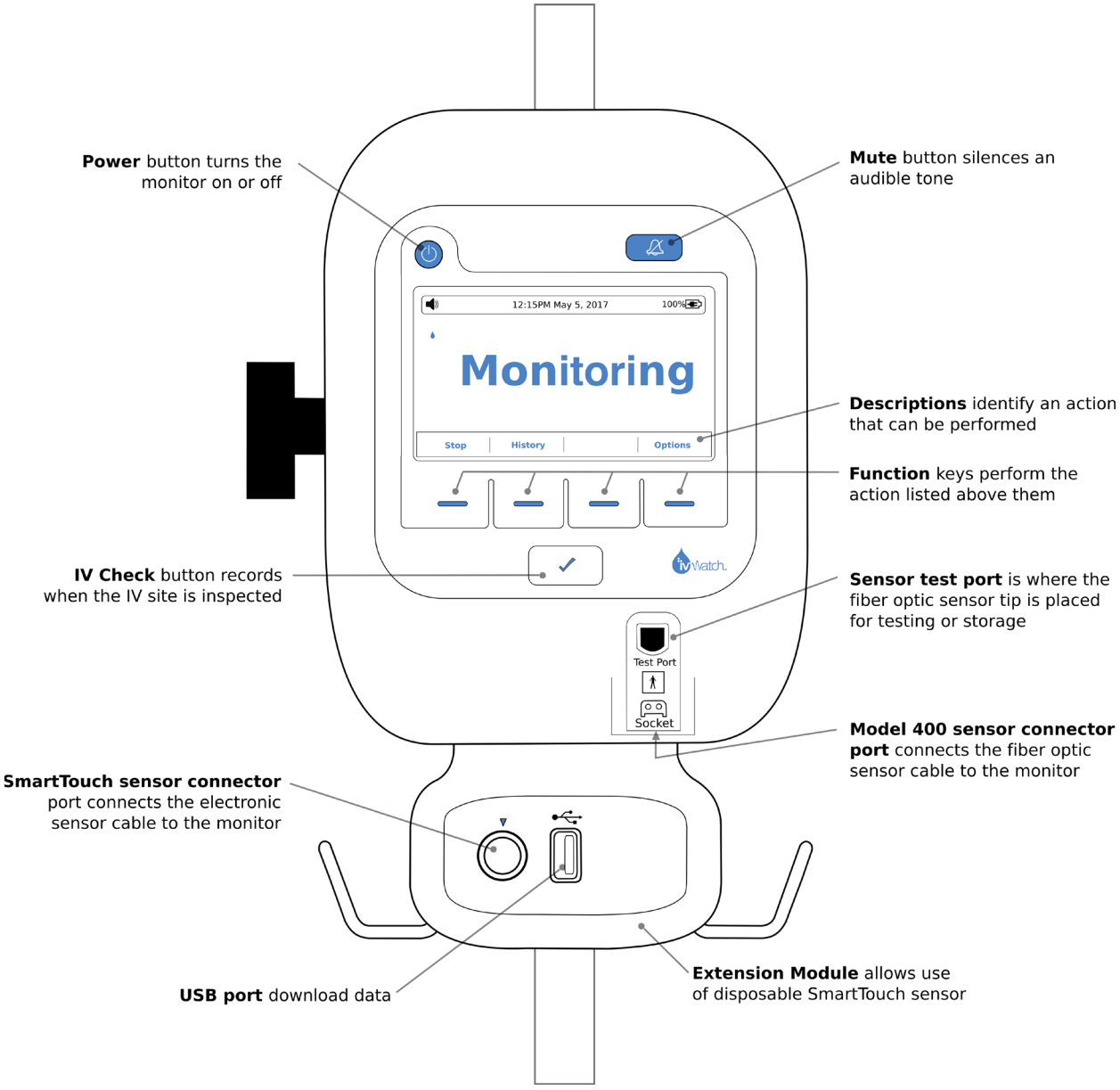


Figure 8. The ivWatch Patient Monitor with extension module and user interface elements.

Methodology

Subject Recruitment

Previous research participants of ivWatch clinical studies will be recruited to participate in the study. Advertisements are not needed to obtain the number of accepted case studies. The study will be limited to healthy adult volunteers (18 years or older). During the initial recruitment, interested participants will be provided an overview of the study and an initial pre-screen will be completed. If eligibility is unclear during the pre-screening process, the registered nurse can consult the chief nursing officer or investigator to determine eligibility. The pre-screening form is

included on page 42. If the participant is interested in the study, 18 years or older, and deemed an acceptable research subject, a time and date for the study will be scheduled with the subject. The formal consent and screening process will be performed on the day of the study, as described in the following section.

Preliminary Information and Consent

The pre-study procedure is listed in detail on page 46. Once arriving at the study site, the subject fills out a sign-in sheet indicating their name and the time of their arrival. The subject is then taken to a private screening room. A research assistant will welcome the subject and provide the informed consent document. The research assistant will discuss the main points of the study and the subject's rights, as described in the consent form.

If the subject understands and signs the consent form, the subject will be asked to fill out a participant health history form. The purpose of the health history form is to prevent potentially sick or unhealthy subjects from participating in the trial. Each subject must complete the health and consent forms before participating in the study. As part of the health history form, the nurse will measure the body temperature of the subject with the goal of preventing sick individuals from participating in the study.

The nurse reviews the subject's health report form to determine if the subject qualifies for the study. A list of exclusion criteria is included in Table 5. Any additional concerns or questions will be directed to the on-staff chief nursing officer and/or medical doctor. They may use their professional judgment to exclude a subject for reasons not included in this list of exclusion criteria.

Table 5. List of study exclusion criteria.

1	Abnormal bleeding / hemophilia
2	Absence of sensation in arms
3	Anemia
4	Cardiopulmonary disorders
5	Clotting disorders
6	Currently pregnant
7	Dehydration
8	Dizziness or fainting
9	Hepatitis
10	HIV / Aids
11	Immune Deficiency Disorders
12	Lymphedema
13	Major surgery or scar tissue which would complicate PIV access
14	Radiation / chemotherapy within last year
15	Received IV therapy in last 14 days
16	Seizures
17	Stroke
18	Sick or had infection in past 14 days
19	High Temperature (>99.6°F)
20	Blood thinning medication (e.g. aspirin regimen, Coumadin, warfarin)
21	Tattoos covering more than half of back of hand or inner forearm

If the subject completes the informed consent document and the health history report form is approved, then the first three sections of the case report form should be completed, which includes general study information, inclusion criteria, and subject information. An example of the case report form is included in the Case Report Form section of this research protocol.

Several metrics of the subject's body are measured as a record of the body type and physiology. These metrics include body weight, height, blood pressure, and circumference of the forearm. The body metrics are recorded in Section 4 of the case report form. The research assistant will also work with the subject to complete a subject pigmentation worksheet. The results of this worksheet are recorded in Section 5 of the case report form.

The selected study configuration information (Table 5) is recorded in Section 6 of the case report form and the serial numbers of the ivWatch patient monitors, extension module, sensor cables, and receptacle are recorded in Section 7 of the case report form.

Data Collection

The data collection checklist is included on page 47. The data collection consists of three processes: (1) subject preparation, (2) data collection, and (3) study completion.

Subject Preparation

Once the preliminary information is collected, the subject will be taken to the test area. The nurse and ultrasound tech will perform hand hygiene and put on latex-free medical-grade gloves. Each subject has two injection sites. The sites are prepared using the same procedure, except one site will use the SmartTouch sensor and one site will use the fiber optic sensor. The nurse and research assistant will examine the potential sites. A photograph of the VeinViewer illumination will be captured as a record of the vascular structure at the site. A second photograph will be captured of the bare site where the injection will occur. This photograph will be compared to a post-study photograph to see if there is any skin irritation associated with the ivWatch sensor. The filenames of these photographs are recorded in Section 7 of the case report form.

Using protocols based on hospital procedures, the nurse cleans the site with a CHG swabstick for 30 seconds and allows to air dry for 30 seconds. The nurse inserts the catheter next to a vein that would typically be used for a PIV therapy. Once the insertion is complete, a shallow high-resolution ultrasound image of the catheter and surrounding tissue is captured. The image should show as much of the catheter length as possible, while also including the catheter tip. The depth of the catheter tip relative to the skin surface is measured and the corresponding image is saved. The ultrasound image File ID and the measured depth are recorded in the case report form.

The nurse places the ivWatch sensor within 5 mm of the approximate location of the catheter tip. After sensor and occlusive dressing placement, the sensor cable and IV tubing are secured to the subject's arm using medical tape.

Once complete, the research assistant will capture a photograph of the dressed site. This photograph can be used to measure the separation between the catheter tip and the ivWatch sensor in a post study analysis. The nurse will measure the circumference of each site. The photograph file ID and circumference are recorded in the case report form.

Data Collection

After both sites have been set up, the nurse will start the data acquisition on the ivWatch patient monitors (t=0). A digital clock is used to record the ivWatch acquisition and infiltration start times. The acquisition start times are recorded in the case report form. The IPMs collect data for 5 minutes.

After the normal acquisition period is complete, the IV pumps are started at their specified rate (either 5, 25, 50, 75, 100, 125, or 150 mL/hr). The pumps will stop automatically after a total of 10mL of isotonic saline is pumped into the subcutaneous tissue. The stop times will be recorded in the case report form. The data acquisition will be stopped on the two IPMs five minutes after the slower of the two infiltrations is complete. The research assistant will record the times of these actions in Section 8 of the case report form.

End of Study

Once the ivWatch data acquisition is complete, additional data is recorded from both sites. First, a post study circumference measurement of the site is performed by the nurse and recorded in the case report form. Then, a photograph is captured of the injection site as a record of the visual swelling. The file identification information of this photograph is recorded in the case report form.

The occlusive dressing and ivWatch sensor are carefully removed from the injection site without pulling out the catheter. The research assistant captures a photograph of the VeinViewer illumination and records the photo ID in the case report form. A series of ultrasound images are captured to record the state of the tissue under the sensor. The file identification information for the ultrasound image is recorded in the case report form. Once the ultrasound imaging is complete, the catheter is removed. Light pressure is applied if there is any bleeding (usually there is no bleeding since this is a subcutaneous injection). A final photograph is captured of the site as a record of skin integrity and whether the ivWatch sensor caused any irritation to the skin. An adhesive bandage is applied to the site.

Once this procedure has been completed for both sites, the research assistant completes the remaining sections of the case report form, which include areas for adding miscellaneous notes, a description of any device deficiencies/malfunctions that occurred, a description of any adverse events that occurred, and an area for an investigator to authorize the case report form. Once the case report form is complete, the subject is taken to the front reception desk and given the participation payment. The subject is asked to sign and date a check-out sheet to verify receipt of payment. A copy of their informed consent form with contact information will be given to the subject should they have any questions or concerns after departing ivWatch.

The research assistant is responsible for cleaning and re-organizing the test area after the subject has departed. This includes removing tape connecting the IV tubing to the ivWatch sensor, disposing the used IV tubing, and cleaning the ivWatch sensor and monitor with hospital-grade disinfectant wipes. Data saved during the study will be removed from the corresponding machines and saved to a secure network server. The data includes IPM data (transferred via USB drive), ultrasound images (transferred via USB drive), and camera images.

The research assistant will store all paperwork from the study (case report forms, subject pigmentation forms) in a manila folder in a secure location. All paperwork containing private health information is given to the HIPAA officer or designee for separate and secure storage.

Data Analysis

After the study is complete, a series of analyses will be performed on the collected ivWatch data. Specific statistical tests and rationale are included in the Statistical Considerations section of this protocol (page 31).

Possible reasons a study may be rejected include, but are not limited to:

1. Equipment (infusion pump, catheter, patient monitor) not operating properly.
2. Leaking catheter or IV site.
3. Early termination by research subject.
4. Sensor placement more than 2 cm from the catheter tip.
5. Significant deviations from research protocol.

All data analyses will be independently reviewed and verified by a second researcher.

Risk Benefit Analysis

Injection of Isotonic Saline

The study design is considered to have minimal risk to the healthy adult volunteers participating in this study. Previous studies have generated infiltrations by intentionally pushing the needle through the vein wall into the surrounding subcutaneous tissue. The placement of the needle into the vein introduces additional risks such as ecchymosis, hematoma, phlebitis, thrombosis, and embolism. This study generates an infiltration by performing subcutaneous injections of isotonic saline solution. This method of generating infiltrations is believed to be much safer for the research subject, including being less painful than puncturing a vein wall.

The most likely complication associated with subcutaneous injections would be an infection. The risk of an infection is reduced by (1) only enrolling healthy adult volunteers (that is, subjects are not immunocompromised) and (2) using safe procedures based on standard hospital practices (PIV therapy) and medical-grade sterile materials (e.g. ultrasound gel, occlusive dressing). Another complication could include hitting a nerve causing significant pain for the subject. This risk is minimized by using an experienced nurse to perform the injections at common sites for PIV therapy.

A registered nurse or physician with significant PIV therapy experience will perform all of the injections and will be onsite throughout the study. ivWatch, LLC has two medical doctors available by phone should any medical related questions arise during a study.

Infusion of saline solution into the subcutaneous tissue does not pose a significant risk to the study subjects. Hypodermoclysis is a common medical practice of injecting saline into subcutaneous tissues for treatment or prevention of dehydration. This is typically used for elderly patients. Hypodermoclysis is performed on a variety of sites including back, abdomen, and upper regions

of the arms and legs. Pump rates range from 20 to 125mL/hr with a total delivered volume less than 1500mL in a 24 hour period [10]. In comparison to the hypodermoclysis procedure, the study's 10mL maximum volume and 5 to 150 mL/hr flow rates of 0.9% saline do not pose a significant health risk to the study subjects.

The ivWatch Technology

The ivWatch technology is a non-significant risk device as determined by the FDA. In a face-to-face meeting with the FDA on March 28, 2014, the FDA classified the ivWatch Model 400 as a Class II, NSR device. The ivWatch Model 400 has received marketing clearance from the FDA for adults and pediatrics. Early prototypes of the Model 400 were evaluated in previous clinical studies with IRB approval. A list of these studies is included in Table 6.

The electronic sensor is designed to perform identically to the Model 400 fiber optic sensor. The materials used for the electronic sensor are common medical grade materials and are generally regarded as safe. The amount of LED light emitted by the sensor into the patient's skin is significantly less than the maximum permissible ocular and skin exposures published in the ANSI Z136.1 Laser safety standard. To our knowledge, there is no standard regulating the safety of LED emitting products, so the laser safety standard has been used to demonstrate the safety of the emitted optical powers. The amount of heat generated by the LEDs in the sensor head is much lower than conventional pulse oximeters, due to a low duty cycle and optical power, as well as an optimized photodiode amplification circuit.

Table 6. Clinical trials involving the ivWatch technology.

STUDY	SPONSOR	INVESTIGATOR	IRB NO.
Healthy adult volunteer study & nurse focus group	CW Optics	University of Virginia Medical Center	HIC11383
Adult patient study	CW Optics	Virginia Commonwealth University Medical Center	HM12146
Pediatric Study	ivWatch, LLC	Cincinnati Children's Hospital Medical Center	2009-2550
NIR Detection of PIV Infiltration	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00008513
The Signal Variation of Normal Tissue	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00008218
The Effect of Catheter Depth	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00008254
The Effect of Infiltration Rate	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00008941
Long Term Adhesion of the ivWatch Receptacle	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00008891
Device Validation for Non-Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00009175
Device Validation for Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00009285
The Effect of Sensor-to-Catheter Distance	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00010217
Infiltration Detection when Placing Over the Dressing	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00013715
Performance for Non-Infiltrated Tissues when Placing Over Transparent Occlusive Dressing	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00015068
Optical Detection of Intravenous Infiltration: A Pilot Study	ivWatch, LLC	Cincinnati Children's Hospital Medical Center	2015-0896
ivWatch SmartTouch Sensor: Monitoring Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00023891
ivWatch SmartTouch Sensor: Signal Variation of Normal Tissue	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00023277
ivWatch SmartTouch Sensor: Device Verification for Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00030567
ivWatch SmartTouch Sensor: Device Verification for Non-Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00030569

ivWatch SmartTouch Sensor: Device Verification for Non-Infiltrated Tissues, Part II	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00032326
ivWatch SmartTouch Sensor: The Effect of PIV Depth and Site	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB ID: 00032269

Follow-Up

There is no anticipated need for a follow-up protocol after this study. Prior to departure, the research personnel will provide the subject with contact information should they have any questions or concerns after leaving the study.

Data Management and Statistical Considerations

Data Management

The data management process includes recording data during the study, transferring data to a secure electronic database, and data validation.

Five forms of data are recorded during each study:

1. Information on the health of the study subject is recorded in the health history form. This form is provided in the Participant Health History Form section of this document. This form is completed by the subject prior to the study. The form requests only information relevant to the study. The health history form is stored in a locked filing cabinet at the ivWatch facility.
2. Study-related information is recorded using the study's case report form (including the subject activity log). The case report form includes study information (gender, age, body measurements, skin classification, product serial numbers, times, and filenames).
   This form is completed by the research assistant during the study. The case report form does not include any personal identifiers. The original forms are stored at the ivWatch facility.
3. The ivWatch data is recorded using the investigational device that store the data internally. The filename does not contain any personal identifiers.
4. The ultrasound images are saved to the ultrasound machine during the study. The filename does not contain any personal identifiers.
5. Digital photographs and video images are recorded throughout the study. The filenames do not contain personal identifiers although the subjects may be identifiable in the images. The informed consent form discloses the collection of photographic images and video recordings.

Once a study is complete, the case report form data, the ivWatch data, ultrasound images, and camera images are transferred to an electronic database. The ultrasound and photographic images are deleted from the ultrasound machine and digital camera, respectively. The database

has been designed such that no personal identifiers are available to match a study dataset with a particular subject. To protect the confidentiality and integrity of the data, the password-protected database can only be accessed by authorized users. The privileges of each authorized user are set by the database administrator. All changes made to the database are recorded in an audit log. The log includes (but is not limited to) which fields were changed and which user made the changes. This audit trail is necessary for data integrity as well as meeting regulatory guidelines. Double data entry by two people is used to verify that data is correctly entered into the database. After validation is complete, the database will be available to the authorized users.

Statistical Considerations

The goal of this study is to validate the performance of the ivWatch SmartTouch sensor for detecting the early stages of an IV infiltration, as collected from healthy adult volunteers. The Model 400 Fiber Optic sensor is used for performance comparison. The study objectives include:

Primary Objective: Demonstrate a statistically significant improvement for detecting early stage infiltrations in comparison to hourly observation by a perfect clinician.

Secondary Objectives:

1. Demonstrate statistical equivalence in infiltration detection volume of the SmartTouch and Fiber Optic sensors.
2. Demonstrate statistical equivalence in infiltration sensitivity of the SmartTouch and Fiber Optic sensors.

Primary Objective

The primary objective is to demonstrate a statistically significant improvement in the sensitivity for early stage infiltrations compared to the current nursing standard of care, where the performance of the current nursing standard is estimated using the concept of a perfect clinician. The perfect clinician assesses the IV site hourly and perfectly classifies the tissue as normal or infiltrated regardless of the volume of fluid that has been infiltrated. The performance of the perfect clinician can be theoretically calculated. For the study configuration listed in Table 7, the perfect clinician would capture 28.2% of the infiltrations prior to an infiltrated volume of 10mL.

Table 7. The study configuration for the infiltration study

Rate (mL/hr)	Number of Subjects	Perfect Clinician Sensitivity (%)	Number of Early Infiltrations Detected by Perfect Clinician
5	14	100.0	14.0
25	14	40.0	5.6
50	14	20.0	2.8
75	14	13.3	1.9
100	14	10.0	1.4
125	14	8.0	1.1
150	14	6.7	0.9

A Monte Carlo simulation was performed to evaluate the hypothesis test comparing the perfect clinician (H_0) and a device with a sensitivity of 90% (H_1). The 90% sensitivity is a conservative assumption based on sensitivities measured in previous ivWatch studies. A total of one million trials were simulated using the study configuration shown in Table 7. The infiltration detection times for the perfect clinician were uniformly distributed between 0 and 60 minutes. The perfect clinician provided early detection of an infiltration if the detection time was less than the time required to infiltrate 10mL at the given rate. The simulation code is included in the Statistical Monte Carlo Analysis Appendix (page 56). Figure 9 shows the results of the Monte Carlo analysis. A threshold of 35% corresponded to an alpha of 0.041 (0.05 was not possible due to the discrete nature of the sampled sensitivities), that is, 95.9% of the null hypothesis trials (perfect clinician) had sensitivities less than 35%.

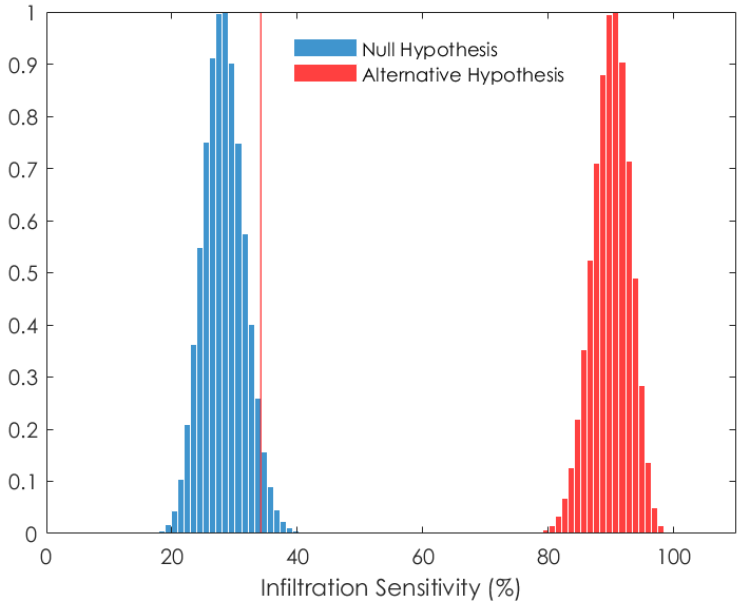


Figure 9. The Monte Carlo simulation of a device operating with an infiltration sensitivity equivalent to the perfect clinician (null hypothesis) and a device operating at a 90% sensitivity (alternative hypothesis). The red line shows the location of a=0.041 threshold (one-sided).

Figure 10 shows the statistical power analysis for this Monte Carlo simulation. A statistical power exceeding 90% was calculated for ivWatch device sensitivities greater than 42%. For the specific alternative hypothesis of 90% sensitivity, the statistical power was estimated to be essentially 100%. A sample size of 98 is assumed in this simulation, which is based on the detection volume comparison objective. In addition to the large statistical power, a sample size of 98 also provides a reasonable confidence interval on our estimated sensitivity. For a sensitivity of 91% (89/98), the 95% confidence interval would be 0.83 to 0.96.

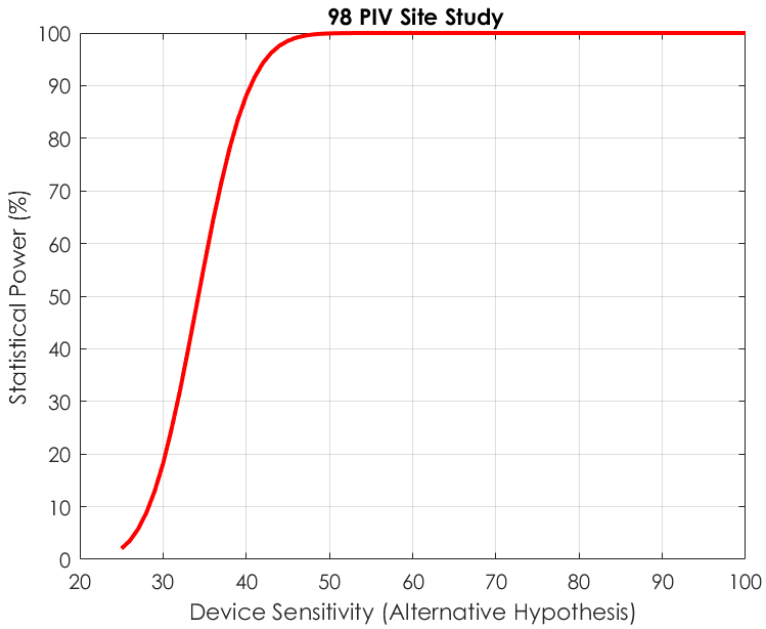


Figure 10. The statistical power for a 98 PIV site study as a function of the device sensitivity (specific alternative hypothesis).

The hypothesis test for a binomial distribution will be performed following the study to ensure the measured sensitivities of both sensors are significantly greater (alpha = 0.05) than the perfect clinician.

Secondary Objectives

Detection Volume Comparison

The first secondary objective is to demonstrate equivalent detection volume between the SmartTouch (ST) and Fiber Optic (FO) sensor. In the clinical study *ivWatch Model 400: Validation for Infiltrated Tissues* (FO sensor), where the same infusion rate configuration from Table 7 was implemented, the mean and standard deviation detection volume was found to be in 3.75 mL ±2.13 mL. In order to test if the mean detection volume for the ST sensor (μ_{ST}) is less than or equal to the mean detection volume of the FO sensor (μ_{FO}) with a margin of error (Δ_0), the following single-sided hypothesis test configuration is used:

Null Hypothesis (H_0): $\mu_{FO} - \mu_{ST} = \Delta_0$

Alternative Hypothesis (H_1): $\mu_{FO} - \mu_{ST} > \Delta_0$

The sample size (n) needed to show equivalence is defined by the following equation:

$$n = \frac{(z_\alpha + z_\beta)^2(\sigma_{FO}^2 + \sigma_{ST}^2)}{(\Delta - \Delta_0)^2}$$

where Δ is the difference in means ($\mu_{FO} - \mu_{ST}$), and σ the standard deviation of each sensor. The σ_{ST} is estimated to be equal to σ_{FO}. The margin of error (Δ_0) is assumed to be 1.0 mL, which is less than half of the standard deviation. An analysis of statistical power versus sample size is shown in Figure 11, (alpha = 0.05). A sample size of 98 subjects will provide a statistical power of 95%. Sample

size for this clinical study is based on this objective. Following the study a single-sided student's t-test will be used to compare the sensor detection volumes.

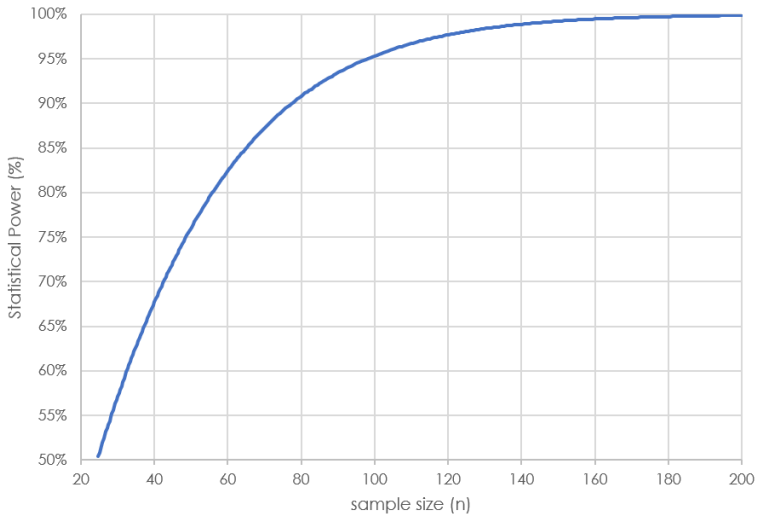


Figure 11. Statistical power vs sample size for detection volume comparison

Sensitivity Comparison

Approximate confidence intervals for the difference in sensor sensitivities ($p_{FO} - p_{ST}$) will be found using the following equation:

$$p_{FO} - p_{ST} - z_{\alpha}\sqrt{\frac{p_{FO}(1-p_{FO})}{n_{FO}} + \frac{p_{ST}(1-p_{ST})}{n_{ST}}} \leq p_{FO} - p_{ST} \leq p_{FO} - p_{ST} + z_{\alpha}\sqrt{\frac{p_{FO}(1-p_{FO})}{n_{FO}} + \frac{p_{ST}(1-p_{ST})}{n_{ST}}}$$

In order for the ST sensor to be equivalent (≥) the FO sensor, the lower bound of the confidence interval should be < 0. Figure 12 illustrates a range of possible confidence intervals in a study with $n_{FO} = n_{ST} = 98$, and a $p_{FO} = 96\%$. In this case, if the ST sensitivity (p_{ST}) is 89% or lower, the lower confidence interval is greater than zero, and the ST sensitivity would be considered significantly less than the FO sensitivity.

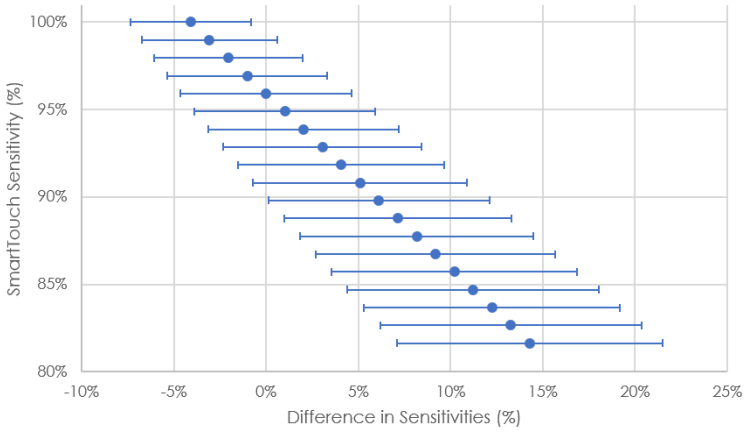


Figure 12. Examples of confidence intervals at various ST sensitivities, assuming FO sensitivity = 96%.

Quality Assurance

As the research sponsor, ivWatch, LLC will continually monitor the research studies to ensure subject safety and data validity. Unlike multicenter studies, all aspects of the study are performed with ivWatch personnel facilitating the quality assurance process.

The first component of the quality assurance program is ensuring the research personnel have the correct training to perform the studies. All study personnel (investigators, research staff, study monitors) will have the proper training (HIPAA and CITI) for conducting clinical trials prior to the start of the study. The subject screening will be performed by a registered nurse.

The second component of the quality assurance program is the monitoring of studies to ensure the procedures outlined in this document are followed. This includes the procedures for data collection (ivWatch research system operation), data storage, and data validation.

The third component of the quality assurance program is monitoring the security of study data. As described in the data management section, study data stored in the database are password protected and restricted to authorized users. Any changes to the database are tracked. The case report forms do not contain subject identifiers. All paper health history forms will be stored in a locked filing cabinet.

Monitoring Plan

The Monitor will complete the initiation of the investigation site prior to beginning the study. Based upon the length and complexity of this study, the Monitor will conduct periodic visits of the investigation site. Minimally, the Monitor will visit the site prior to the closing out the study and complete the Monitoring Visit Checklist and Report using SF-1001020.

Expected Outcomes of the Study

The expected outcome of this study is an understanding of whether the ivWatch SmartTouch sensor will be as effective as the Model 400 for detecting early stage infiltrations.

Publication Policy

ivWatch will approve any publication released as a result of this research study. Results of the study may be published in various healthcare segments relating to vascular access, such as the Infusion Nurses Society and Association for Vascular Access.

Duration of the Study

Each study will last up to approximately 2 hours. The entire study is expected to require less than two months to complete.

Anticipated Problems

Project timing and budgeting difficulties are not anticipated for this research project. First, the study consists of approximately 115 participants (98 accepted case studies). ivWatch is confident the necessary data can be collected from 98 subjects within 1-2 months. Second, the budget for this project is funded by ivWatch, LLC. ivWatch will pay for costs specified in the clinical trial agreement.

Ethics

ivWatch, LLC will follow ethical and regulatory guidelines while conducting this study. The investigators will not proceed with the study until the consent form has been signed by each volunteer subject. Prior to obtaining informed consent signatures, the study will be verbally described to each volunteer and the investigators will address any outstanding questions or concerns. The investigators will receive the proper informed consent training prior to the study. Overall, the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Vulnerable populations will not be targeted for enrollment.

Good Clinical Practice

Good Clinical Practice (GCP) according to the ICH guidelines and ISO 14155 Clinical Investigation of Medical Devices will be followed for this study. In addition, ivWatch clinical investigations follow ICH E6, and FDA 21CFR50,54, 56 and 812.

Clinical Trial Insurance

Insurance is provided to study subjects for medical expenses incurred from bodily injury during clinical testing.

Informed Consent Forms

Please see the attached informed consent form.

Deviations from the Protocol

Investigators will notify the IRB of any deviation from the investigational plan/protocol to protect the life or physical well-being of a subject in an emergency as soon as possible, but not later than five (5) working days after the emergency occurred.

Serious Adverse Events / Device Deficiencies

Serious adverse events and/or device deficiencies are not anticipated, as this general protocol has been followed with this device and other research systems in several previous studies. All serious and unanticipated events will be reported as soon as possible, and no later than ten (10) working days after becoming aware of the event. Other non-serious adverse events and device deficiencies will be recorded in the case report form.

Case Report Form

1. General Study Information

Case Report Form #: _____ **Study Start Date** (MM/DD/YYYY)**:** _____

2. Inclusion Criteria

☐ Signed consent ☐ Subject 18 years or older ☐ Health form approved

3. General Subject Information

Gender: ☐ Male ☐ Female **Age:** _____ years

4. Body Measurements

Weight: _____ lb

Height: _____ in

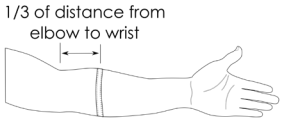
Systolic Blood Pressure: _____ mmHg

Diastolic Blood Pressure: _____ mmHg

Forearm Circumference

Left forearm: _____ mm

Right forearm: _____ mm



5. Skin Pigmentation (Check one)

☐ **Light** ☐ **Medium** ☐ **Dark**

Skin Type Score: _____ **Fitzpatrick Skin Type:** _____

6. Study Configuration

	Left Site	**Right Site**
Sensor *(Select One Per Side)*	☐ Fiber Optic ☐ SmartTouch	☐ SmartTouch ☐ Fiber Optic
Site *(Select One)*	☐ Hand ☐ Forearm	
Infiltration Rate	_____ cc/hr	

CRF# _____

7. Pre-Study Information				
	Left Site		**Right Site**	
SmartTouch™ Sensor Serial No.				
Patient Cable Serial No.				
Extension Module Serial No.				
IPM Serial Number				
Fiber Optic Cable Serial No.				
Fiber Optic Receptacle Lot No.				
Vein Viewer Photo (File ID)				
Pre-Insertion Photo (File ID)				
Ultrasound Images without Calipers (Time)	(In-Plane)	(Out-Plane)	(In-Plane)	(Out-Plane)
Ultrasound Images with Calipers (Time)	(In-Plane)	(Out-Plane)	(In-Plane)	(Out-Plane)
Catheter Depth (mm)	(In-Plane)	(Out-Plane)	(In-Plane)	(Out-Plane)
Post-Insertion Photo (File ID)				
Site Circumference (mm)				

CRF# _____

8. Study Information		
	Left Site	**Right Site**
IPM Start Time (HH:MM:SS)		
Staff Initials (Verify correct pump rate)		
Pump Start Time (HH:MM:SS)		
Pump Stop Time (HH:MM:SS)		
Total Volume Infused (mL)		
IPM Stop Time (HH:MM:SS)		

9. Post-Study Information				
	Left Site		**Right Site**	
Site Circumference (mm)				
Dressed Site Photo (File ID)				
Vein Viewer (File ID)				
Ultrasound Images without Calipers (Time)	(In-Plane)	(Out-Plane)	(In-Plane)	(Out-Plane)
Ultrasound Images with Calipers (Time)	(In-Plane)	(Out-Plane)	(In-Plane)	(Out-Plane)
Catheter Depth (mm)	(In-Plane)	(Out-Plane)	(In-Plane)	(Out-Plane)
Catheter Displacement (mm)				
Bare Site Photo (File ID)				

CRF# _____

10. Miscellaneous Notes

Are there any additional comments related to the case study? Please include comments below.

☐ Yes ☐ No ☐ N/A

11. Device Deficiencies / Malfunctions

Did the investigation device not perform as expected by the intended use when used per the instructions and the protocol?

☐ Yes ☐ No

Could this deficiency/malfunction have led to an adverse event?

☐ N/A ☐ Yes ☐ No

If yes to either question, please explain:

☐ N/A

12. Adverse Events

Did the patient experience any unexpected harm associated with the ivWatch Model 400 device or the research protocol?

☐ Yes ☐ No

Is this event reportable?

☐ N/A ☐ Yes ☐ No

If yes to either question, please explain:

☐ N/A

13. Authorization

I certify that to the best of my knowledge, the information contained in this form is true and correct.

_____ _____
Signature of Investigator Date

_____
Printed Name of Investigator

Pre-Screening Form

Name: (Last) _____ (First) _____ (Middle Initial) _____

Date of Birth: (MM/DD/YYYY) _____

Phone: _____ Email: _____

Medical Questions	Yes*	No
1. Do you have any allergies?		
2. Are you currently participating in any other medical studies?		
3. Do you have a history of fainting when needles are used on you?		
4. Are you taking any medications?		
5. Have you been hospitalized in the past 14 days?		
6. Have you been sick or had an infection in the past 14 days?		
7. Have you received IV therapy in the past 14 days?		
8. Do you have tattoos covering more than half of your inner forearms or back of your hands?		
9. Do you have significant scar tissue on your inner forearms or back of your hands?		
10. Do you have an absence of sensation in your arms?		
11. (For females only) Are you currently pregnant?		☐N/A
*If yes to any of the above, please explain: ☐N/A		

Medical History					
Condition	**Yes***	**No**	**Condition**	**Yes***	**No**
Bleeding Disorder			Immune Deficiency Disorders		
Cardiopulmonary Disorders			Lymphedema		
Clotting Disorders			Radiation/Chemotherapy		
Currently anemic			Seizures/Epilepsy		
Hepatitis			Stroke		
HIV/Aids			Tuberculosis		
*If yes to any shaded areas above, please explain: ☐N/A					
If you have any other medical conditions we should be aware of, please explain below.					
If yes, please explain: ☐N/A					

Eligible ☐ Ineligible ☐ **ivWatch Staff Signature _____ **Date**_____

****If "yes" is checked for any of the shaded "Yes" boxes and there isn't acceptable reasoning, the subject is ineligible. If you are unsure about the subject's eligibility, consult the physician/nurse on staff to determine eligibility.**

Notes from consultation:

_____
Date

_____
Time

_____
Consulted physician/nurse

☐N/A

Health History Form

Name: (Last) _____ (First) _____ (Middle Initial) _____

Date of Birth: (MM/DD/YYYY) _____

Address: (Street) _____

(City) _____ (State) _____ (Zip) _____

Phone: _____ Email: _____

Medical Questions	Yes*	No
1. Do you have any allergies?		
2. Are you currently participating in any other medical studies?		
3. Do you have a history of fainting when needles are used on you?		
4. Are you taking any medications?		
5. Have you been hospitalized in the past 14 days?		
6. Have you been sick or had an infection in the past 14 days?		
7. Have you received IV therapy in the past 14 days?		
8. Do you have tattoos covering more than half of your inner forearms or back of your hands?		
9. Do you have significant scar tissue on your inner forearms or back of your hands?		
10. Do you have an absence of sensation in your arms?		
11. (For females only) Are you currently pregnant?		☐N/A

*If yes to any of the above, please explain:

☐N/A

Medical History					
Condition	**Yes***	**No**	**Condition**	**Yes***	**No**
Bleeding Disorder			Immune Deficiency Disorders		
Cardiopulmonary Disorders			Lymphedema		
Clotting Disorders			Radiation/Chemotherapy		
Currently anemic			Seizures/Epilepsy		
Hepatitis			Stroke		
HIV/Aids			Tuberculosis		

*If yes to above, please explain:

☐N/A

If you have any other medical conditions we should be aware of, please explain below.

If yes, please explain:

☐N/A

Temperature: _____ ˚F

Eligible ☐ Ineligible ☐ **ivWatch Staff Signature _____ **Date** _____

****If "yes" is checked for any of the shaded "Yes" boxes and there isn't acceptable reasoning, the subject is ineligible. If you are unsure about the subject's eligibility, consult the physician/nurse on staff to determine eligibility.**

_____
Date

_____
Time

_____
Consulted physician/nurse

Notes from consultation:

☐N/A

Skin Pigmentation Worksheet

Skin Pigmentation Worksheet

CRF Number: _____

Reaction to Sun Exposure					
Score	**0**	**1**	**2**	**3**	**4**
What happens when you stay in the sun too long?	Painful redness, blistering, peeling	Blistering followed by peeling	Burns sometimes followed by peeling	Rare burns	Never had burns
To what degree do you turn brown?	Hardly or not at all	Light color tan	Reasonable tan	Tan very easy	Turn dark brown quickly
Do you turn brown within several hours after sun exposure?	Never	Seldom	Sometimes	Often	Always
How does your face react to the sun?	Very sensitive	Sensitive	Normal	Very resistant	Never had a problem

Total Score for Reaction to Sun Exposure: _____

Tanning Habits					
Score	**0**	**1**	**2**	**3**	**4**
When did you last expose your body to sun (or artificial sunlamp/tanning cream)?	More than 3 months ago	2-3 months ago	1-2 months ago	Less than a month ago	Less than 2 weeks ago
Did you expose the area to be treated to the sun?	Never	Hardly ever	Sometimes	Often	Always

Total Score for Tanning Habits: _____

Skin Pigmentation Worksheet

CRF Number: _____

Genetic Disposition					
Score	**0**	**1**	**2**	**3**	**4**
What is the color of your eyes?	Light Blue, Gray, Green	Blue, Gray or Green	Blue	Dark Brown	Brownish Black
What is the natural color of your hair?	Sandy Red	Blond	Chestnut/ Dark Blond	Dark Brown	Black
What is the color of your skin (non-exposed areas)?	Reddish	Very Pale	Pale with Beige tint	Light Brown	Dark Brown
Do you have freckles on unexposed areas?	Many	Several	Few	Incidental	None

Total Score for Genetic Disposition: _____

Add up the total scores for each of the three sections for your Skin Type Score.

Skin Type Score	Fitzpatrick Skin Type
0-7	I
8-16	II
17-25	III
26-30	IV
over 30	V-VI

My Skin Score _____ My Skin Type _____

Pre-Study Checklist

CRF#: _____

Step	Role	Status	Task
1.	Subject		Sign in at the reception desk and show identification.
2.	Research Assistant		Subject taken to private screening room.
3.	Research Assistant		Provide informed consent form with description of the study.
4.	Research Assistant		Discuss study and ask if the subject has questions regarding the study and/or their rights as a participant.
5.	Subject		Review and either sign consent form or opt-out of study.
6.	Research subject		Take subject to health screening room.
7.	Nurse		Provide health history form to subject.
8.	Subject		Complete health history form.
9.	Nurse		Ask subject if they have questions regarding the health history form. Measure body temperature of the subject and record at the bottom of the form.
10.	Nurse		Review the completed health history form. If a section is marked "yes," confirm the subject has provided an explanation. If necessary, consult with the physician on staff for sections marked as "yes" and determine the subject's eligibility.
11.	Nurse		If health history form is accepted, complete Sections 1-3 of the Case Report Form.
12.	Nurse		Perform health screening of the subject to measure weight, height, blood pressure, and forearm circumference. Record measurements in Section 4 of the Case Report Form.
13.	Nurse		Work through the Subject Pigmentation Worksheet with the subject. Calculate the final score for the subject and record in Section 5 of the Case Report Form.
14.	Nurse		Use personal judgement to determine the skin tone of the subject and record in Section 5 of the Case Report Form.
15.	Nurse		If the subject has passed the health history form and Sections 1-6 are completed in the Case Report Form, take subject to the test area.

Data Collection Checklist

CRF#: _____

Step	Role	Status	Task
1	Research Assistant		Subject taken to test room. Ensure subject comfort.
2	Nurse		Nurse and ultrasound tech to perform hand hygiene. Apply latex-free gloves.
3	Research Assistant		Review Sections 1-6 of the case report form.
4	Research Assistant		Record the serial/lot numbers of the ivWatch equipment in Section 7 of the case report form.
5	Nurse		On the Fiber Optic IPM, set up the run and verify the cable is functioning properly. The IPM should show the placement screen.
Prepare Site on Left Arm			
6	Nurse		If necessary, shave the site location.
7	Research Assistant		Photograph VeinViewer illumination at site. Record File ID of VeinViewer Photograph in Section 7 of case report form.
8	Research Assistant		Photograph bare site. Record File ID of Pre-Insertion Photograph in Section 7 of the case report form.
9	Nurse		Clean selected area on subject with CHG Swabstick for 30 seconds and allow to air dry for 30 seconds.
10	Nurse		Place catheter tip next to a vein typically used for IV therapy. If needed, use ultrasound during placement. Discard needle in sharps container.
11	US Tech		Record post-insertion ultrasound images of injection site. • Capture in-plane ultrasound image of catheter and measure depth of catheter tip. • Capture out-of-plane ultrasound image of catheter and measure depth of catheter tip. • Record ultrasound file IDs (time) and catheter depth in section 7 of the case report form. If images are in the same minute, label the second image with "a". • Remove ultrasound gel from site using gauze and clean area with two alcohol wipes.
12	Nurse		Connect IV Tubing to Catheter • Remove air from catheter hub using normal saline. • Connect IV tubing to catheter. • Dry area around catheter using gauze. • Place a piece of tape over catheter to hold in place.
13	Nurse		The configuration is **not over** dressing. a. Apply occlusive dressing over injection site. b. Adhere ivWatch sensor on the same side of the vein as the catheter while using spare catheter for placement. c. Verify sensor is approximately 5 mm from the catheter.
14	Nurse		Perform cable management and secure sensor cable to IV tubing using medical tape.
15	Nurse		Check that the sensor is connected to the corresponding ivWatch patient monitor (IPM).

16	Research Assistant		Photograph monitoring site. Record File ID of Post-Insertion Photograph in Section 7 of case report form.
Prepare Site on Right Arm			
17	Research Assistant		Photograph VeinViewer illumination at site. Record File ID of VeinViewer Photograph in Section 7 of case report form.
18	Research Assistant		Photograph bare site. Record File ID of Pre-Insertion Photograph in Section 7 of the case report form.
19	Nurse		Clean selected area on subject with CHG Swabstick for 30 seconds and allow to air dry for 30 seconds.
20	Nurse		Place catheter tip next to a vein typically used for IV therapy. If needed, use ultrasound to place the catheter. Discard needle in sharps container.
21	US Tech		Record post-insertion ultrasound images of injection site. • Capture in-plane ultrasound image of catheter and measure depth of catheter tip. • Capture out-of-plane ultrasound image of catheter and measure depth of catheter tip. • Record ultrasound file IDs and catheter depth in section 7 of the case report form. If the images are in the same minute, label the second image with "a". • Remove ultrasound gel from site using gauze and clean area with two alcohol wipes.
22	Nurse		Connect IV Tubing to Catheter • Remove air from catheter hub using normal saline. • Connect IV tubing to catheter. • Dry area around catheter using gauze. • Place a piece of tape over catheter to hold in place.
23	Nurse		The configuration is **not over** dressing. a. Apply occlusive dressing over injection site. b. Adhere ivWatch sensor on the same side of the vein as the catheter while using the spare catheter for placement. c. Verify sensor is approximately 5 mm from the catheter.
24	Nurse		Perform cable management and secure sensor cable to IV tubing using medical tape.
25	Nurse		Check that the sensor is connected to the corresponding ivWatch patient monitor (IPM).
26	Research Assistant		Photograph monitoring site. Record File ID of Post-Insertion Photograph in Section 7 of case report form.
27	Nurse		Clean ultrasound probe by wiping thoroughly with Sani-Cloth Wipe.

Data Collection				
28	Nurse		Site Circumference Measurement. Mark a line on the dressing indicating where to place the measuring tape, such that the circumference is measured at the approximate location of the catheter tip. Complete this on both arms. Record Site Circumferences in Section 7 of case report form.	
29	Nurse		Start data acquisition on IPMs. Using the digital clock, record acquisition start time in Section 8 of case report form.	t = 0 min
30	Nurse		Start IV pumps. Record start times in Section 8 of case report form.	t = 5 min
31	Nurse		Record stop times in Section 8 of case report form.	10 mL infiltrated
32	Nurse		Stop data acquisition on IPM. Record acquisition stop time (digital clock) in Section 8 of case report form.	5 minutes after both pumps stopped
33	Nurse		Measure circumference of the subcutaneous injection sites on both arms using previous markings. Record Site Circumferences in Section 9 of the case report form.	
34	Research Assistant		Begin data transfer on the IPMs.	
Left Arm Post Study Assessment				
35	Research Assistant		Photograph monitoring site. Record File ID of Dressed Site Photograph in Section 9 of case report form.	
36	Nurse		Remove occlusive dressing and ivWatch sensor from site. Mark location of sensor head.	
37	Research Assistant		Photograph VeinViewer illumination at site. Record File ID of VeinViewer Photograph in Section 9 of case report form.	
38	US Tech		Record ultrasound images of injection site after infiltration complete. • Capture in-plane ultrasound image of catheter and measure catheter depth. • Capture out-of-plane ultrasound image of catheter and measure catheter depth. • Record ultrasound file IDs and catheter depth in section 9 of the case report form. If the images are in the same minute, label the second image with "a". • Remove ultrasound gel from site using gauze. • Measure displacement between catheter tip and sensor. Record in Section 9 of case report form.	
39	Nurse		Remove catheter. Apply light pressure until bleeding stops. Try not to displace infiltrated fluid.	
40	Research Assistant		Photograph bare site for record of skin integrity. Record File ID of Bare Site Photograph in Section 9 of case report form.	
41	Nurse		Apply adhesive bandage to site.	
Right Arm Post Study Assessment				
42	Research Assistant		Photograph monitoring site. Record File ID of Dressed Site Photograph in Section 9 of case report form.	
43	Nurse		Remove occlusive dressing and ivWatch sensor from site. Mark location of sensor head.	
44	Research Assistant		Photograph VeinViewer illumination at site. Record File ID of VeinViewer Photograph in Section 9 of case report form.	

45	US Tech		Record ultrasound images of injection site after infiltration complete. • Capture in-plane ultrasound image of catheter and measure catheter depth. • Capture out-of-plane ultrasound image and measure catheter depth. • Record ultrasound file IDs and catheter depth in section 9 of the case report form. If the images are in the same minute, label the second image with "a". • Remove ultrasound gel from site using gauze. • Measure displacement between catheter tip and sensor and record in Section 9 of case report form.
46	Nurse		Remove catheter. Apply light pressure until bleeding stops. Try not to displace infiltrated fluid.
47	Research Assistant		Photograph bare site for record of skin integrity. Record File ID of Bare Site Photograph in Section 9 of case report form.
48	Nurse		Apply adhesive bandage to site.
49	Nurse		Clean ultrasound probe by wiping with Sani-Cloth Wipe.
Study Completion			
50	Research Assistant		Complete Sections 10-13 in case report form.
51	Research Assistant		Take subject to front reception desk and provide study participation payment. Provide a copy of the patient's ICF should they have questions after leaving.
52	Subject		Sign and date the check-out sheet to verify receipt of payment. The subject leaves.
53	Research Assistant		Remove tape connecting IV tubing and sensor cable. Dispose of the IV tubing. Clean the ivWatch sensor with hospital-grade disinfectant wipes. Bundle the cable and store on the IV pole.
54	Research Assistant		Clean the test area.
55	Research Assistant		Transfer the following to the network server: 1. ivWatch Data (via USB drive) 2. Ultrasound Images (via USB drive) 3. Camera Images
56	Research Assistant		Store paperwork (case report form and checklists) in manila folder. Provide paperwork containing private health information to HIPAA officer for separate and secure storage.

FDA Clearance Letters for ivWatch Model 400

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

February 13, 2015

ivWatch, LLC
Javier Garriz
Vice President of Product Management
469 McLaws Circle
Williamsburg, VA 23185

Re: K142374
Trade/Device Name: ivWatch Model 400
Regulation Number: 21 CFR 880.5725
Regulation Name: Accessories, Pump, Infusion
Regulatory Class: Class II
Product Code: MRZ
Dated: January 16, 2015
Received: January 20, 2015

Dear Mr. Garriz:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

Page 2 – Javier Garriz

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Susan Runner DDS, MA

Erin Keith
Director
Division of Anesthesiology,
General Hospital, Respiratory, Infection
Control, and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

December 22, 2016

ivWatch, LLC
Jaclyn Lautz
Director of Regulatory Affairs and Quality Assurance
1100 Exploration Way, Suite 209
Hampton, Virginia 23666

Re: K162478
Trade/Device Name: ivWatch Model 400
Regulation Number: 21 CFR 880.5725
Regulation Name: Infusion Pump
Regulatory Class: Class II
Product Code: PMS
Dated: November 22, 2016
Received: November 28, 2016

Dear Jaclyn Lautz:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

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Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely,

Tina Kiang, Ph.D.
Acting Director
Division of Anesthesiology,
General Hospital, Respiratory,
Infection Control, and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Investigator Signatures

Example [I certify that I am knowledgeable about the regulations and policies governing research with human subjects. I have reviewed this document and agree to conduct the study in accordance with the approved protocol.]

Principal Investigator

Name: William J. Naramore

Signature:

Date:

Investigator

Name: Susan Brown, MSN, MSED, BA, VA-BC

Signature:

Date:

Investigator

Name: Gregory J. Schears, M.D.

Signature:

Date:

Investigator

Name: Marisa A. Cole

Signature:

Date:

Statistical Monte Carlo Analysis

```
clear variables;
close all;
clc;

% Parameters of the Monte Carlo Simulation
simulation.number_of_trials = 1000000;
simulation.alternative_hypothesis_sensitivity = 0.90;

% Perform the Monte Carlo Simulation (method included below)
results = simulate_study2(simulation);

% Generate figure of simulated distributions
figure;
h(1) = bar(results.bins, results.null_sensitivities_bins/max(results.null_sensitivities_bins));
hold on;
h(2)                                    =                                    bar(results.bins,
results.alternative_sensitivities_bins/max(results.alternative_sensitivities_bins));
set(h(2),'FaceColor','r');
set(get(h(1),'Children'),'EdgeAlpha',0)
set(get(h(2),'Children'),'EdgeAlpha',0)
set(get(h(1),'Children'),'FaceAlpha',0.5)
set(get(h(2),'Children'),'FaceAlpha',0.5)
xlim([0 110])
xlabel('Infiltration Sensitivity (%)')
h_legend = legend('Null Hypothesis', 'Alternative Hypothesis');
set(h_legend,'Location','NorthWest')
children = get(h_legend,'Children');
alt_box = get(children(1),'Children');
null_box = get(children(3),'Children');
set(alt_box,'FaceAlpha',0.5);
set(null_box,'FaceAlpha',0.5);
set(alt_box,'EdgeAlpha',0);
set(null_box,'EdgeAlpha',0);
set(h_legend,'EdgeColor',[1 1 1]);
hold on;
plot(results.threshold*[1 1], [0,1],'r-')

% Printe statistical metrics to MATLAB console
fprintf(1,'Threshold:   %f   (%f   H0   cases   below   this   threhsold)\r',   results.threshold,
results.confidence);
fprintf(1,'Statistical Power (1-Beta): %f\r', results.power);
fprintf(1,'Alpha: %f (one-sided)\r', results.alpha);
fprintf(1,'Beta: %f\r',results.beta);
fprintf(1,'Mean Null: %f', results.mean_null);

% Generate plot showing statistical power as a function of the sensitivity
% of the alternative hypothesis
alternative_hypotheses = [0.25:0.01:1];
h = waitbar(0,'Please be patient Jason');
for i=1:length(alternative_hypotheses)
    simulation.alternative_hypothesis_sensitivity = alternative_hypotheses(i);
    results = simulate_study2(simulation);
    powers(i) = results.power;
    waitbar(i/length(alternative_hypotheses),h);
end
close(h);
figure;
plot(alternative_hypotheses*100,100* powers,'r-');
xlabel('Device Sensitivity (Alternative Hypothesis)');
ylabel('Statistical Power (%)');
title('70 PIV Site Study')
grid

% Save figure
%gtb_save_figure(figure(1),'MonteCarloAnalysis')
%gtb_save_figure(figure(2),'StatisticalPowerAnalysis')
```

```
function [results] = simulate_study2(simulation)

% Load study simulation details
number_of_trials = simulation.number_of_trials;
number_of_subjects = 90;
% Load the alternative hypothesis sensitivity (predicted sensitivity of
% ivWatch device)
alternative_hypothesis_sensitivity = simulation.alternative_hypothesis_sensitivity;

% The volume limit
Vlim = 10;

% List of rates
rates = [5; 25; 50; 75; 100; 125; 150];

% Detection by the perfect clinician is uniformly distirbuted between 0 and
% 60 minutes

for i=1:number_of_trials
    % Detection times uniformly distributed between 0 and 60 minutes
    detection_matrix_null = 60*rand(7,14);

    % The perfect clinician detects the infiltration if
    % (detection_matrix_null)<Vlim/R*60
    sensitivity_matrix_null = detection_matrix_null < Vlim./repmat(rates,1,14)*60;

    % Sensitivity for the perfect clinician for this particular trial
    null_sensitivities(i)                                                    =
sum(sensitivity_matrix_null(:))/length(sensitivity_matrix_null(:))*100;

    % Generate matrix with uniformly distributed numbers between 0 and 1.
    sensitivity_matrix_alt = rand(7,14);

    % Sensitivity for the ivWatch device for this particular trial
    alternative_sensitivities(i)                                             =
sum(sensitivity_matrix_alt(:)<alternative_hypothesis_sensitivity)            /
length(sensitivity_matrix_alt(:))*100;
end

% Bin the results
bins = (1:number_of_subjects)/number_of_subjects*100;
null_sensitivities_bins = hist(null_sensitivities,bins);
alternative_sensitivities_bins = hist(alternative_sensitivities,bins);

% Figure out a threshold where > 95% of the clinician sensitivities are
% less than this threshold
null_cumsum = cumsum(null_sensitivities_bins)./ sum(null_sensitivities_bins);
pos = find(null_cumsum > 0.95);
threshold = (bins(pos(1))+bins(pos(1)+1))/2;

% Calculate statistical metrics
power = sum(alternative_sensitivities_bins(bins > threshold))/sum(alternative_sensitivities_bins);
alpha = sum(null_sensitivities_bins(bins > threshold))/sum(null_sensitivities_bins);
beta = sum(alternative_sensitivities_bins(bins < threshold))/sum(alternative_sensitivities_bins);

% Output results
results.threshold = threshold;
results.confidence = 1-alpha;
results.power = power;
results.alpha = alpha;
results.beta = beta;
results.bins = bins;
results.null_sensitivities_bins = null_sensitivities_bins;
results.alternative_sensitivities_bins = alternative_sensitivities_bins;
results.mean_null = mean(null_sensitivities);
```

Bibliography

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