Optical Detection of Intravenous Infiltration: A Pilot Study – Phase II

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Abstract

Pediatric patients are a high-risk population for intravenous (IV) infiltration due to their activity level, limited communication skills, and small limb size. An IRB-approved clinical study was performed to measure the performance of the ivWatch Model 400 device for detecting early stage infiltrations on pediatric patients under the age of 18. The device uses visible and near-infrared light to detect changes in the optical properties of subcutaneous tissue that are consistent with infiltrated fluid. 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 non-alarming group, the device issued red "Check IV" notifications an average time of 29.8 hours (95% confidence interval: 14.8 to 44.8 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% (95% confidence interval: 56.5% to 92.5%). In the alarming group, the device issued notifications for 12 out of 15 clinician-confirmed infiltrations (95% confidence interval: 51.9% to 95.7%). The device issued notifications approximately once every 4 days for subjects without clinician-confirmed infiltrations. The results from this study show that the ivWatch device can aid clinicians in identifying infiltrated tissue, decreasing patient harm and improving patient safety.

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1 Background / Introduction

Peripheral intravenous (IV) therapy is one of the most common invasive procedures performed in 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 IV therapy. A multicenter trial measured an infiltration rate of 27-32 events per 1000 intravenous catheter days [2]. 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 [3].

Pediatric patients are a high-risk population for infiltration due to their activity level, limited communication skills, and small limb size. 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 [4, 5]. Severe infiltration or extravasation may lead to necrosis requiring skin debridement, skin grafting, or amputation [6]. Infiltration rate is independent of infusion rate and it does not vary significantly with regard to injection site, catheter size, or catheter type [7].

Current nursing practice involves periodic IV site assessments for continuous infusions. The IV site assessment includes identifying swelling, pain, redness, warmth, or coolness. Cincinnati Children's Hospital Center Medical Center (CCHMC) has been a leader in developing assessment methods for prevention of IV infiltrations. The assessment methods include bundling four major components: (1) consistent hourly IV site assessment using touch-look-compare (TLC), (2) an evidence-based three-tier medication tissue toxicity list, (3) best practice alerts for high risk infusates in the medication administration record, and (4) shift-to-shift report that includes bedside IV site assessment. Despite implementation of this four-component "IV bundle", sustaining low rates of infiltration and extravasation injuries is a challenge in many pediatric institutions [8, 9, 10].

The ivWatch Model 400 is an FDA-cleared medical device intended to aid healthcare professionals in monitoring patients at least 18 years old for IV infiltration and extravasation using a near infrared (NIR) light sensor. The ivWatch signal is sensitive to changes in the optical properties of the underlying tissue. An infiltration or extravasation event leads to a decrease in the optical scattering properties due to the introduction of a low-scattering infusate into the subcutaneous tissue. The ivWatch sensor is placed on the skin within a few centimeters of the approximate location of the IV catheter tip, and continuously monitors the IV site for signs of infiltration or extravasation.

2 Study Objectives

The primary goal of this study was to measure the performance of the ivWatch Model 400 for detecting infiltrated IV sites on pediatric patients. This study was designed to measure several important metrics that describe the performance of the ivWatch device. These metrics include:

(1) device sensitivity – how many of the clinician-confirmed infiltrations are detected by the ivWatch device?
(2) time to detection – does ivWatch reduce the time to when an infiltration is detected?
(3) the notification rate – how often does the ivWatch device issue infiltration-related notifications?

3 Methods

Pediatric patients at CCHMC with anticipated IV therapy duration greater than 24 hours were targeted for enrollment in the study. The age requirement for the study was neonate to 17 years

old, with a weight requirement of greater than 2.5 kg. All subjects received standard care for their IV sites including routine assessments by the bedside registered nurses (RN). Subjects also had an ivWatch device monitoring the IV site. This study was approved by the CCHMC Institutional Review Board. Informed consent and assent were performed according to CCHMC protocols.

The study was divided into three groups: pilot, non-alarming, and alarming.

3.1 Pilot Group

The first 10 subjects were enrolled in the pilot group. A non-alarming ivWatch device monitored the IV sites of these subjects. The goal of this small pilot study was to give clinicians an opportunity to perform the protocol and operate the ivWatch device and to give investigators the opportunity to make adjustments prior to starting the subsequent non-alarming group.

3.2 Non-Alarming Group

In the non-alarming group, the ivWatch device monitored IV sites, but did not issue infiltration notifications. The data collected from subjects in this group allowed the researchers to estimate the difference in time to detection between the ivWatch device and hospital's standard nursing practices, and the sensitivity of the device to clinician-confirmed infiltrations.

3.3 Alarming Group

In the alarming group, IV sites were monitored with the ivWatch device, and visible/audible infiltration notifications were enabled. This study group allowed researchers to estimate the notification rate (the number of infiltration notifications issued in a given period of time) as well as the infiltration size and severity when ivWatch notifications are available to alert clinicians to the early stages of an infiltration.

3.4 IV Site Assessment

For all subjects, CCHMC nurses regularly assessed the IV site according to hospital procedures. If an infiltration or other complication with the IV therapy was identified, the infusion was stopped and the nurse informed a research assistant from the vascular access team (VAT) to perform final IV site assessment and complete the case study.

In the alarming group, the ivWatch device issued yellow and red notifications when the measured signal suggested an IV site infiltration may have occurred. As described in the device instructions for use, the yellow infiltration notification is an early warning indicating that the signal levels at the site are starting to appear like an infiltration is occurring. Yellow infiltration notifications can be automatically dismissed by the ivWatch device if the signal returns to normal levels. A red infiltration notification indicates that the signal conditions indicate a greater probability that an infiltration has occurred. Once a red notification is issued, the ivWatch monitor is locked in the red state until a clinician can assess the site. In the alarming group, if a red infiltration notification was issued by the ivWatch device, the research assistant made an assessment of the IV site.

If an infiltration was confirmed by the research assistant from the VAT, the IV therapy was stopped and standard CCHMC protocols for handling infiltration and extravasation events were followed. If no infiltration was evident, the research assistant restarted the ivWatch device. The research assistant and bedside RNs then continued to perform his/her normal IV site assessments.

3.5 Sample Size

The size of the non-alarming and alarming groups was calculated to be 150 subjects each, in order to capture a minimum of five clinician-confirmed infiltrations with a statistically significant

difference between ivWatch and clinician time-to-detection. A detailed statistical power analysis is included in the research protocol (Appendix A).

4 Results

4.1 Data Sets Analyzed

There were 156 subjects enrolled in the non-alarming group, and 57 subjects enrolled in the alarming group, for a total of 213 subjects. The number of subjects included in the non-alarming group is 156 rather than the expected 150, because the pilot group was joined in with the non-alarming group (due to no protocol differences). The number of subjects in the alarming group was 57 rather the expected 150. This is because the sample size calculation is based on the number of clinician-confirmed infiltrations. Fifteen (15) clinician-confirmed infiltrations were observed after 57 subjects, where the 150-subject sample size calculation assumed 5 clinician-confirmed infiltrations. Since more than sufficient statistical power is estimated with 15 infiltrations, the investigators decided to complete the alarming group at 57 subjects.

4.2 Demographics

Appendix C includes a complete listing of the subject attributes, including age, gender, weight, and monitoring location for the accepted case studies. As illustrated in Figure 1, 99 males and 114 females were enrolled in the study. A similar proportion of males and females is seen in the non-alarming and alarming groups.

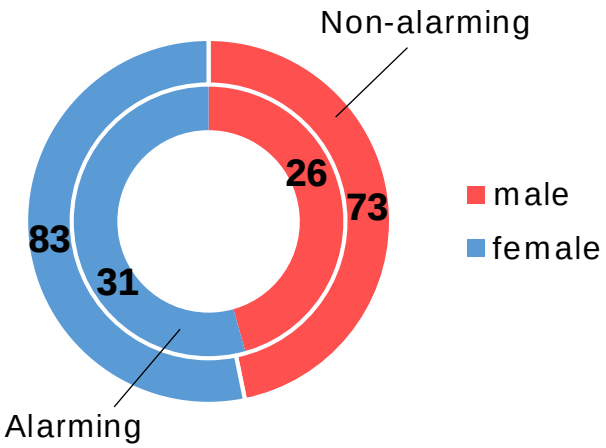

Figure 1. Gender for all subjects, where the outside and inside rings show proportions of the non-alarming and alarming groups, respectively

The distribution of skin pigmentations is illustrated in Figure 2. Twenty-seven of the subjects had dark pigmentation, 20 subjects had medium pigmentation, and the remaining 166 subjects had light pigmentation (Figure 2). A similar proportion of skin colors is seen in the non-alarming and alarming groups.

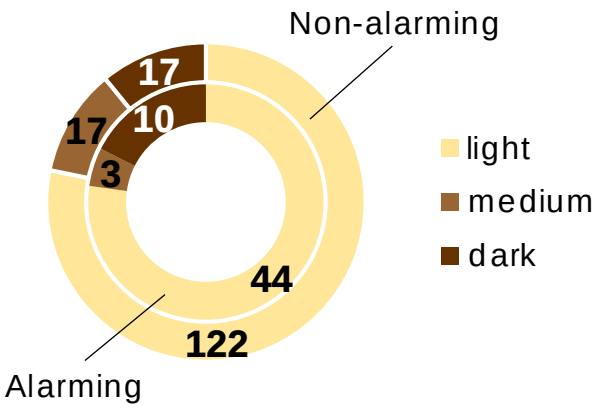

Figure 2. Skin pigmentation for all subjects, where the outside and inside rings show proportions of the non-alarming and alarming groups, respectively

The distribution of subject ages is illustrated in Figure 3. The ages ranged from 2 weeks to 17 years, with an average age of 7.4 years. Ages of less than 2 years were recorded in units of months. The distribution of age in subjects less than 2 years is shown in Figure 4.

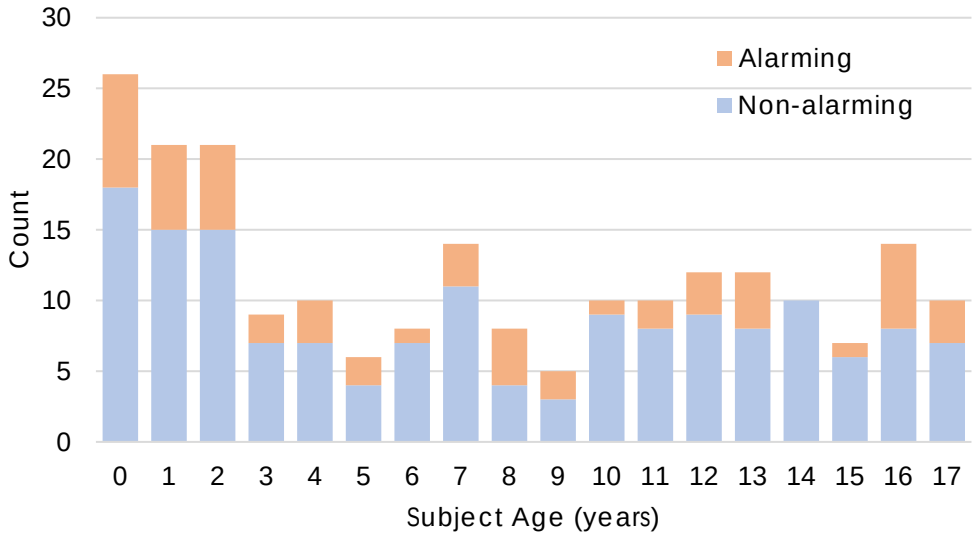

Figure 3. Age distribution of all accepted case studies (n = 213).

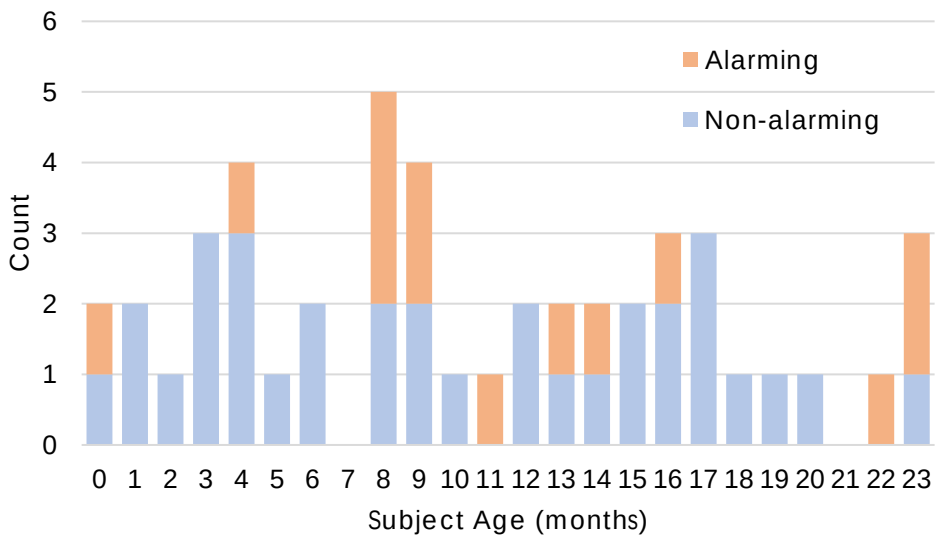

Figure 4. Age distribution of the accepted case studies less than 24 months old (n = 47).

4.3 Efficacy Results

4.3.1 Analysis of Efficacy

Three key metrics are presented in the efficacy analysis:

1. *Infiltration Sensitivity (Non-Alarming and Alarming Groups)* - The infiltration sensitivity is defined as the percentage of the clinician-confirmed infiltrations that are detected by the ivWatch device before the clinician's diagnosis. This metric is measured and reported separately for non-alarming and alarming groups, since an infiltration notification by the ivWatch device could bias the clinician's diagnosis.

2. *Time Difference between Detections (Non-Alarming Group)* - The difference in time to detection between the clinician and the ivWatch device is measured from the non-alarming group. This measurement reveals how much earlier the infiltration could have been detected by the ivWatch device compared to the clinician assessments. This metric is measured using the patients in the non-alarming group since an infiltration notification by the ivWatch device could bias the clinician's diagnosis.

3. *Notification Rate (Alarming Group)* - The notification rate is defined as the number of ivWatch device infiltration notifications issued in a certain amount of time, typically reported in units of notifications per day. The notification rate is a combination of both false and true notifications – the false notification rate cannot be accurately determined with no gold standard available for comparison. This metric is measured using the subjects in the alarming group since the number of notifications could potentially depend on how quickly nurses reset the device.

4.3.2 Non-Alarming Group

A total of 23 clinician-confirmed infiltrations occurred in 156 subjects of the non-alarming group. This corresponds to an infiltration rate of 14.7% for the non-alarming study population.

Infiltration Sensitivity

The ivWatch device would have issued a red Check IV notification for 18 out of 23 clinician-confirmed infiltrations of the non-alarming group. The device sensitivity and confidence intervals stratified by IV site is shown in Table I. The confidence intervals are calculated using binomial distribution with the Clopper-Pearson method. In every ivWatch-detected infiltration case, both a yellow and red Check IV notification would have been issued, so the sensitivity is equivalent for yellow and red Check IV notifications.

Table I. ivWatch Sensitivity for clinician-confirmed infiltrations in the non-alarming group

	Clinician Detected (n)	ivWatch Detected (n)	ivWatch Sensitivity (%)	95% Confidence Interval	
				Lower Limit	Upper Limit
All Sites	23	18	78.3%	56.5%	92.5%
Hand and Forearm Sites	20	16	80.0%	56.3%	94.3%
Other Sites - AC, Foot, and Leg	3	2	66.7%	9.4%	99.1%

Time Difference between Detections

The time difference between the red Check IV notification and the clinician identification of an infiltration was between 1.3 and 99.8 hours in the ivWatch-detected cases. On average, the ivWatch device issued a red Check IV notification 29.8 hours prior to clinician detection, with a 95% confidence interval of 14.8 to 44.8 hours using the student's t-distribution. A yellow Check IV notification was issued an average of 32.3 hours prior to clinician detection, with a 95% confidence interval of 17.3 to 47.3 hours. In every clinician-confirmed infiltration where a red Check IV notification was issued, at least one yellow Check IV notification was issued prior to the red. Table II lists the time difference for each subject.

Table II. Difference in time between ivWatch device and clinician detection of infiltration events in the non-alarming group (n/a denotes non-detected by ivWatch)

CRF	Site	Yellow Check IV time difference (hours)	Red Check IV time difference (hours)
6	Leg	n/a	n/a
9	Forearm	1.4	1.3
23	Hand	13.9	12.9
29	Foot	42.9	33.0
36	Forearm	n/a	n/a
37	Forearm	100.5	99.8
75	Hand	9.4	2.4
78	Forearm	18.3	15.9
84	Forearm	14.6	14.5
92	Hand	n/a	n/a
101	AC	27.2	12.0
111	Hand	n/a	n/a
114	Hand	29.2	29.2
130	Hand	n/a	n/a
142	Hand	60.2	59.4
150	Hand	2.1	1.4
152	Forearm	43.8	43.8
155	Hand	7.1	5.3
160	Forearm	1.5	1.5
163	Hand	81.6	81.2
166	Hand	9.0	8.9
167	Hand	51.0	49.4
171	Forearm	67.2	64.6

Figure 5 shows a histogram of the distribution of the time differences between red Check IV notifications and clinician detection. The distribution appears to be skewed, with many of the time differences in the 0 to 20-hour range. Since larger time differences influence the average calculation, the median time between ivWatch detection and clinician detection may be more appropriate for describing the difference between device detection and clinician detection. The median time between ivWatch notifications and clinician detection was 15.2 and 22.8 hours for red and yellow Check IV notifications, respectively.

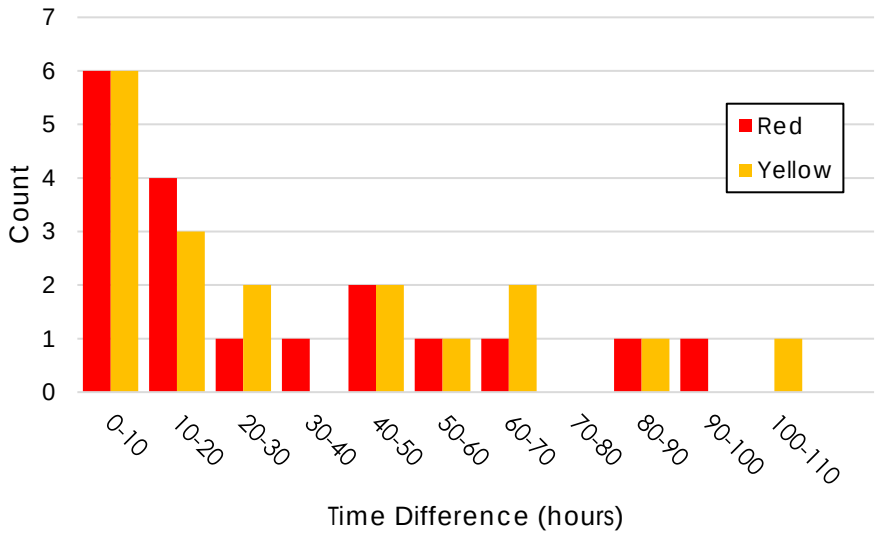

Figure 5. Distribution of time difference between red and yellow ivWatch notifications and clinician detection of infiltration events

4.3.3 Alarming Group

A total of 15 clinician-confirmed infiltrations occurred in 57 subjects of the alarming group. This corresponds to an infiltration rate of 26.3% for the alarming group study population.

Infiltration Sensitivity

The ivWatch device issued a yellow and red notification in 12 of the 15 clinician-confirmed infiltrations for the alarming group. This corresponds to 80% sensitivity, and a 95% confidence interval from 51.9% to 95.7% using the Clopper-Pearson method.

Notification Rate

The notification rates excluding clinician-confirmed infiltrations are an estimate of the false positive performance of the ivWatch device, because the false notification rate cannot be accurately determined with no gold standard available for comparison. Negative binomial regression is utilized to obtain an estimation of the likelihood of red and yellow Check IV notifications that were not connected to clinician-confirmed infiltrations. Since each subject is monitored for a different amount of time, an "offset" term is included in the model, which is equal to the natural log of the subject specific total followup time during which a notification may have occurred. The data used for this regression model is included in Appendix D.

The notification rate of all cases in the alarming group, excluding clinician-confirmed infiltrations, is shown in Table III. These notification rates correspond to approximately 1 notification every 4 days.

Table III. Notification rates for all subjects in the alarming group, excluding clinician-confirmed infiltrations

		95% Confidence Interval	
	Estimated Rate	Lower Limit	Upper Limit
	alarms/day	*alarms/day*	*alarms/day*
Red Notifications	0.280	0.156	0.500
Yellow Notifications	0.274	0.119	0.631

The IV's of two subjects were terminated because of a painful flush, after a clinician response to a red or yellow Check IV notification. For these two subjects, the ivWatch device may have detected infiltrated fluid, while the clinician identified a bad IV, but not a visible infiltration. Table IV shows the estimated notification rates excluding these two subjects.

Table IV. Notification Rates for all subjects in the alarming group, excluding clinician-confirmed infiltrations and IV termination because of painful flushes

		95% Confidence Interval	
	Estimated Rate	Lower Limit	Upper Limit
	alarms/day	*alarms/day*	*alarms/day*
Red Notifications	0.268	0.146	0.492
Yellow Notifications	0.206	0.089	0.477

A red or yellow notification can be caused by device-related issues as well. Table V lists the subjects where device-related issues where identified.

Table V. Identified device-related issues

Case Report Form #	Description of Device-Related Issue
207	Subject found lying on cable
208	Sensor cable strain relief bent significantly by another device mounted to IV pole below
209	Sensor cable strain relief bent significantly by another device mounted to IV pole below
214	Sensor removed from receptacle
217	Receptacle de-adhesion from skin
219	Receptacle taped over
242	Broken cable(s) and receptacle de-adhesion from skin

Table VI shows the notification rate for the alarming group, excluding subjects where a possible device issue was identified. When excluding these subjects, the notification rates are estimated at 1 notification every 10 days.

Table VI. Notification Rates for all cases in the alarming group, excluding clinician-confirmed infiltrations, painful IV's, and identified device-related issues.

		95% Confidence Interval	
	Estimated Rate	Lower Limit	Upper Limit
	alarms/day	*alarms/day*	*alarms/day*
Red Notifications	0.103	0.042	0.251
Yellow Notifications	0.077	0.027	0.221

4.4 Safety Results

Adverse events were recorded in the study for CRF numbers 100 and 120. The CRF 100 event was skin irritation observed near the receptacle at the antecubital fossa (AC) joint. In the CRF 120 event, skin blanching was observed under the receptacle, which appears to have been placed on the subject's wrist. Both were recorded as "mild non-serious events". A more detailed description of the events is provided in Appendix E.

5 Discussion and Conclusion

5.1 Early Detection of Infiltrations

The ivWatch Model 400 is intended as an aid to clinicians for continuous monitoring and early detection of infiltrations. In the non-alarming group, the median time between ivWatch device and clinician detection of infiltration events was 15.2 hrs, with a range of 1.3 hrs to 99.8 hrs. This data supports that the ivWatch technology can detect infiltration before it is visible by eye or detectable by other IV assessment techniques. Early detection of infiltration events helps to reduce patient harm by minimizing the volume of IV fluid potentially leaking into surrounding tissue.

5.2 Analysis of the Volume of Infiltrations

Although the exact volume of infiltrated fluid is unknown in this study, the swelling percent recorded by CCHMC can be used as a relative measurement of volume. The swelling percent metric used by CCHMC in the documentation of infiltration events, and is defined as the length of the swelling in its longest dimension divided by the length of the arm (see Case Report Form in Appendix A). The length of swelling is estimated by the VAT research assistant by palpation and visual observation.

The swelling percent was recorded for most of the clinician confirmed infiltrations in this study (Table VII). The median swelling percent for the non-alarming and alarming groups were 36% and 21%, respectively. In 5 of the 12 detected infiltrations in the alarming group, the clinician terminated the IV within one hour of the red Check IV notification (highlighted in Table VII(b)). The median swelling percent was 16% for these 5 cases. In the other 7 detected cases in the alarming group, the clinician restarted monitoring with the ivWatch device after a red Check IV notification, and the infiltration was eventually found and confirmed by a clinician. In these 7 cases, the swelling percent recorded reflects the infiltration at the time when the clinician was able to confirm the infiltration. It can be estimated that there was almost no (0%) visible swelling at the IV site when the ivWatch device issued a notification.

Table VII. Infiltration swelling percent in the (a) non-alarming group and (b) alarming group (highlighted rows show cases when the nurse terminated the IV within an hour of the red Check IV notification)

(a) Non-Alarming Group		
CRF #	Swelling %	Time between red notification and clinician detection (hr)
6	49	n/a
9	37	1.3
23	56	12.9
29	16	33.0
36	17	n/a
37	58	99.8
75	not recorded	2.4
78	36	15.9
84	3	14.5
92	39	n/a
101	21	12.0
111	16	n/a
114	30	29.2
130	22	n/a
142	not recorded	59.4
150	46	1.4
152	14	43.8
155	42	5.3
160	43	1.5
163	57	81.2
166	13	8.9
167	35	49.4
171	36	64.6
Median	36	14.6

(b) Alarming Group		
CRF #	Swelling %	Time between red notification and clinician confirmation (hr)
197	16	0.6
198	21	9.7
203	70	2.5
205	27	0.2
210	19	12.5
216	9	0.1
218	42	17.6
220	38	n/a
224	not recorded	n/a
226	15	7.0
230	23	1.7
232	17	0.3
235	0	3.7
239	44	n/a
240	7	0.8
Median	21	2.1

5.3 False Positive Performance

An estimate of the false positive performance of the ivWatch Model 400 is given by the notification rate where a clinician-confirmed infiltration was not observed. The ivWatch device has also been tested in controlled 'motion' studies, where healthy adult subjects were monitored with the ivWatch device for a 24-hour period in a simulated hospital environment [11]. Subjects in the motion study did not receive IV therapy, so the tissue monitored by the ivWatch device was truly non-infiltrated. As compared to this pediatric study (see Table III above), similar notification rates were observed in the adult motion study as shown in Table VIII below. In both studies, a red notification is estimated to occur once every 4 days.

Table VIII. Notification rates for ivWatch motion study in healthy adults

		95% Confidence Interval	
	Estimated Rate	Lower Limit	Upper Limit
	alarms/day	*alarms/day*	*alarms/day*
Red Notifications	0.255	0.104	0.622
Yellow Notifications	0.526	0.193	1.435

5.4 Conclusions

Results from this pediatric study have shown the benefits of using the ivWatch technology for early detection of infiltration. The ivWatch device was sensitive to early infiltration events, and alerted clinicians of infiltrations hours before they were detected by clinician assessment. This device can aid clinicians in identifying infiltrated tissue early, in order to decrease patient harm and improve patient safety.

6 References

[1] E. M. Kagel and G. M. Rayan, "Intravenous catheter complications in the hand and forearm," *J Trauma-Injury Infection & Crit Care,* vol. 56, no. 1, pp. 123-127, Jan 2004.

[2] C. M. Rickard, J. Webster, M. C. Wallis, N. Marsh, M. R. McGrail, V. French, L. Foster, P. Gallagher, J. R. Gowardman, L. Zhang, A. McClymont and M. Whitby, "Routine versus clinically indicated replacement of peripheral intravenous catheters: a randomised controlled equivalence trial," *Lancet,* vol. 380, pp. 1066-1074, 2012.

[3] D. T. Gault, "Extravasation injuries," *Br J Plast Surgery,* vol. 46, no. 2, pp. 91-96, Mar 1993.

[4] J. Pettit, "Assessment of Infant with a Peripheral Intravenous Device," *Adv Neonatal Care,* vol. 3, no. 5, 2003.

[5] M. Legemaat, P. J. Carr, R. M. Rens, M. van Dijk, I. E. Poslawsky, and A. van den Hoogen, "Peripheral intravenous cannulation: complication rates in the neonatal population: a multicenter observational study," *J Vasc Access*, vol. 17, no. 4, pp. 360-365, Jul 2016.

[6] S. Phelps and R. A. Helms, "Risk factors affecting infiltration of peripheral venous lines in infants," *J Pediatr,* vol. 111, no. 3, pp. 384-389, Sep 1987.

[7] J. E. Jacobs, B. A. Birnbaum, C. P. Langlotz, "Contrast media reactions and extravasation: Relationship to intravenous injection rates," *Radiol.,* vol. 176, pp. 411-416, 1998.

[8] B. F. Tofani, S. A. Rineair, C. H. Gosdin, P. M. Pilcher, S. McGee, K. R. Varadarajan, P. J. Schoettker, "Quality improvement project to reduce infiltration and extravasation events in a pediatric hospital," *J Pediatr Nurs*, vol. 26, no. 6, pp. 682-689, Dec 2012.

[9] E. Clark, B. K. Giambra, J. Hingl, D. Doellman, B. Tofani, and N. Johnson, "Reducing risk of harm from extravasation: a 3-tiered evidence-base list of pediatric peripheral intravenous infusates," *J Infus Nurs*, vol. 36, no. 1, pp. 37-45, Jan-Feb 2013.

[10] S. A. Rineair and D. Doellman, "Taking Pediatric Assessments to the Next Level," Poster presented at: Infusion Nurses Society Annual Meeting, May 2016, Fort Lauderdale, Fl.

[11] ivWatch LLC, 2014, "ivWatch Model 400: Device Validation for Non-Infiltrated Tissues (IVW400CS-09)," unpublished internal document.

Appendix A Study Protocol

Research Protocol

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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 the infusate leaks 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. In this protocol, the term infiltration is intended to represent both infiltration and extravasation events. Pediatric patients are a high-risk population for infiltration due to their activity level, limited communication skills, and small limb size. Current nursing practice involves regular PIV site assessments for continuous infusions. The PIV site assessment includes identifying swelling, pain, redness, warmth, or coolness. If an infiltration or extravasation is identified, the infusion is stopped and treatment may be performed. Early recognition of an infiltration can minimize patient harm.

ivWatch, LLC has developed the ivWatch Model 400 – a Class II device that has obtained FDA 510(k) clearance for use on adults. The ivWatch Model 400 is indicated for the detection of infiltrations and extravasations of 10cc or less of optically clear infusates, as an adjunctive device to the clinical evaluation in the hospital setting of patients 18 years old or greater with peripherally-inserted IVs (PIVs) on the forearm or dorsal aspect of the hand. This study will examine the use of the ivWatch Model 400 to monitor PIV sites in pediatric patients. The data collected will be analyzed after study completion and compared with observations made by nurses in the hospital.

The primary goal of this phase II pilot study is to measure the performance of the ivWatch Model 400 for detecting infiltrated PIV sites on pediatric patients. The monitoring device to be assessed includes the latest technological advances developed since phase I of this study.

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General Information

Protocol Title:

Optical Detection of Intravenous Infiltration: A Pilot Study – Phase II

Name and Address of Sponsor:

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Sponsor Contact:

Garret Bonnema, Ph.D., Chief Science Officer

Name and Title of Investigators:

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Rationale and Background

Peripheral intravenous therapy (PIV) 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. A multicenter trial published in 2012 indicated infiltrations occurred 27-32 times per 1000 intravenous catheter days in adults [2]. 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 [3].

Pediatric patients are a high-risk population for infiltration due to their activity level, limited communication skills, and small limb size. 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 [4]. Current nursing practice involves hourly PIV site assessments for continuous infusions. The PIV site assessment includes identifying swelling, pain, redness, warmth, or coolness. 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 infiltration rate is independent of infusion rate and it does not vary significantly with regard to injection site, catheter size, or catheter type [7].

ivWatch, LLC has developed a class II medical device that has received FDA clearance to aid medical professionals in monitoring adult patients for PIV infiltration and extravasation using a near infrared (NIR) light sensor. The ivWatch signal is sensitive to changes in the optical properties of the underlying tissue. An infiltration or extravasation event leads to a decrease in the optical scattering properties due to the addition of a low-scattering infusate into the subcutaneous tissue.

The ivWatch Model 400 has been tested in a series of seven IRB-approved studies on healthy adult research subjects, as summarized in Table 1. The design verification studies consisted of the first five studies to evaluate 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 notifications when monitoring normal, non-infiltrated tissues. Two clinical studies evaluated how the infiltration rate (*The Effect of Infiltration Rate*) and catheter depth (*The Effect of Catheter Depth*) affected the diagnostic performance of the ivWatch Model 400. The device detected all 10 mL 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 had a reduced sensitivity by the device. The final study titled *Long Term Adhesion of the ivWatch Receptacle* 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 minimal contribution to clinical alarm fatigue.

In Phase I of this pilot study, there were 5 infiltrations detected out of 127 accepted case studies. An algorithm developed on this study successfully detected 100% of the infiltrations prior to the nurse's diagnosis. Based on the results from phase I and other clinical studies, technological improvements were made to the device, which is cleared for use on adults.

Phase II of this study is to evaluate the performance of these technological improvements in the ivWatch Model 400 for pediatric patients.

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Table 1. 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 hours 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. 4. 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

Study Goals and Objectives

The primary goal of this phase II pilot study is to measure the performance of the ivWatch Model 400 for detecting infiltrated PIV sites on pediatric patients. This study shares the same objectives as the phase I pilot study:

- Comparing whether the ivWatch device can help nurses detect infiltrations earlier relative to the standard of care,
- Comparing detection rates of infiltration events between current nursing practice and the ivWatch Model 400 device,
- User satisfaction for clinician and patient.

Study Design

The study has been designed to measure several important metrics that describe the performance of the device. These metrics include:

(1) **time to detection** – does ivWatch reduce the time to when an infiltration is detected,
(2) **device sensitivity** – how many of the nurse confirmed infiltrations are detected by the ivWatch device,
(3) **the notification rate** – how often does the ivWatch device issue infiltration-related notifications.

Pediatric patients (neonates weighing more than 2.5 kg to adults) will be enrolled who will have continuous IV therapy with an anticipated duration greater than 24 hours. As illustrated in Figure 1, the study will be divided into three groups and consist of approximately 340 patients to obtain 310 accepted case studies. All subjects will receive standard care for their IV sites including the normal routine assessments of the IV site by the bedside registered nurses. Subjects will also have an ivWatch device monitoring the site that may or may not issue infiltration notifications depending on the subject's assigned study group. Sensor monitoring and ambient light errors will be issued in all cases to communicate to clinicians when data is not being properly recorded.

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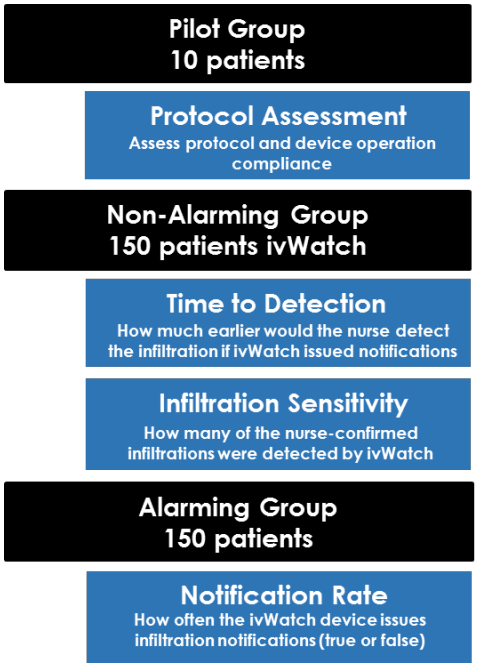

Figure 1. The study design.

The first 10 subjects will be enrolled into the pilot group. A non-alarming ivWatch device will monitor the IV sites of these subjects. The goal of this small pilot study is to give clinicians an opportunity to perform the protocol and operate the ivWatch device and to give researchers the ability to make adjustments prior to starting the subsequent non-alarming group. Significant changes to the research protocol will be submitted to the IRB for approval.

Once the pilot group is complete, the next 150 patients will be enrolled in the non-alarming group. The ivWatch device will monitor the IV sites but will not issue infiltration notifications. The subjects in this group will allow researchers to estimate the difference in time to detection between the ivWatch device and standard nursing practices and the sensitivity of the device to nurse-confirmed infiltrations.

The final 150 patients will be enrolled in the alarming group. The IV sites will be monitored with the ivWatch Model 400 infiltration notifications enabled. This means the device will issue visual and audible notifications when the signal suggests an IV site has become infiltrated. This study group will allow researchers to estimate the notification rate (the number of infiltration notifications issued in a given period of time) and the infiltration size and severity when ivWatch notifications are available to alert clinicians to the early stages of an infiltration.

The size of the non-alarming and alarming groups was calculated to be 150 subjects in order to capture a minimum of five nurse-confirmed infiltrations. If less than 5 infiltrations have been recorded after 150 patients, a request to the IRB for more subjects will be submitted to ensure that a minimum of 5 infiltrations are recorded in each group. A discussion on using a target of five infiltrations is included in the Statistical Power Analysis section of this research protocol.

If the research subject is deemed acceptable and is interested in participating in the study, an investigator will discuss the study with the patient and their parent(s) or legal guardian(s). The

informed consent / informed assent process will be performed according to the procedures and language defined by CCHMC. Once entered into the study, various metrics of each subject will be recorded, as summarized in Figure 2. These metrics include the weight, height, forearm circumference, and skin classification. These metrics may be transcribed from the patient record, when appropriate. A post-study analysis will be performed to identify correlations between the measured signal and anatomical/physiological characteristics of the research subjects.

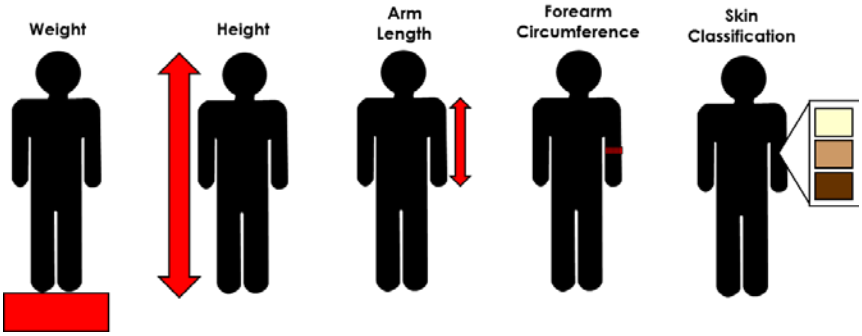

Figure 2. Pre-study measurements performed on each subject.

The placement of the catheter will be performed according to the existing hospital procedures. Once the catheter is in the vein and secured to the patient, the ivWatch sensor / receptacle will be adhered next to the site. The placement of the ivWatch sensor and receptacle is illustrated in Figure 3. Care will be taken to place the sensor as close as possible to the catheter tip while (1) not obscuring the site for assessment by clinicians and (2) not placing the sensor directly over a large vein.

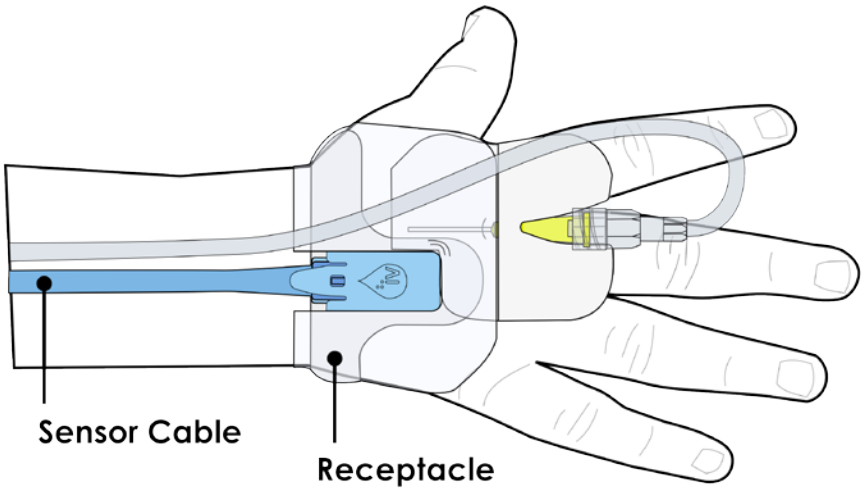

Figure 3. Examples of the ivWatch sensor and receptacle.

A standard occlusive dressing typically used by the hospital will be placed over the catheter site. An additional ivWatch occlusive dressing will be placed over the ivWatch sensor and receptacle according to the placement protocol (Appendix A). The additional dressing reinforces the adhesion of the ivWatch receptacle to the patient. Photographs of the dressed site will be

captured to record the position of the sensor with respect to the catheter. The ivWatch sensor 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 patient using medical tape following standard hospital procedures and ivWatch instructions for use. The time of PIV placement, catheter size, and any difficulty in catheter placement will be noted in the case report form.

The proximal end of the ivWatch sensor will be connected to the ivWatch patient monitor (IPM). A rendering of the patient monitor is included in Figure 4. The rendering identifies the user interface elements on the front face of the IPM. The IPM logs data during the study and is attached to the IV pole. Once the ivWatch receptacle and sensor have been placed on the subject, the research assistant will start the data acquisition using the device's instructions for use. The ivWatch device will collect data throughout the PIV therapy. Patients in the non-alarming group will be monitored with ivWatch patient monitors that have the infiltration-related notifications disabled. Patients in the alarming group will be monitored with ivWatch patient monitors that have visible and audible infiltration-related notifications enabled.

For all groups in the study, the device will issue sensor monitoring or ambient light errors to indicate issues with recording data for the subject. Sensor monitoring errors are issued when the sensor cable is detached from tissue or if there are large rapid changes in the ambient light that degrade the performance of the ivWatch measurements. Ambient light errors occur if the ambient light is so intense that it blinds the detection circuitry of the ivWatch patient monitor.

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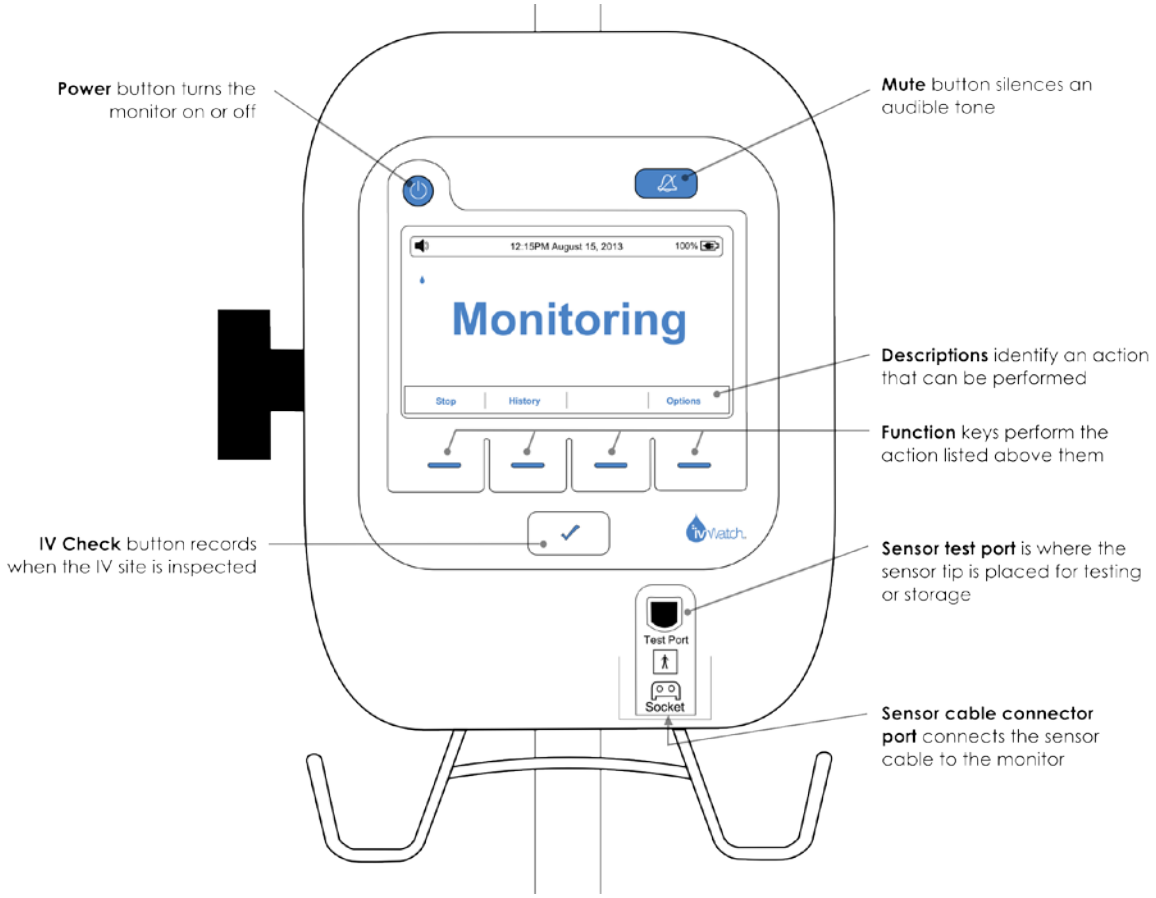

Figure 4. The ivWatch Patient Monitor (Model 400) and user interface elements.

CCHMC nurses will assess the site regularly according hospital procedures. After each assessment, the nurse will press the *IV Check* button on the ivWatch device to record the assessment time in the ivWatch data. The *IV Check* button is illustrated in Figure 4. If an infiltration or other complication with the IV therapy is identified, the infusion will be stopped and the nurse will inform a research assistant before removing the catheter.

At the end of therapy, a small saline flush will be performed to IVs that appear normal to ensure the catheter was located in the vein. The catheter will be removed from the patient and a last set of measurements and photographs will be recorded of the site. The photographs are used to assess whether the ivWatch sensor receptacle caused any skin irritation or disruption to the skin integrity (i.e. tearing or removal of skin layer). If an infiltration was identified by the nurse or research assistant, measurements of the swollen area will be performed and the infiltration will be graded according to hospital procedures. These infiltration measurements will be recorded in the case report form.

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Methodology

Study Personnel

Table 2 describes the three roles associated with the study. There are four investigators who are responsible for the overall conduct of the study. These investigators may perform any of the duties associated with the study, including those duties specified for research assistant or nurses (where applicable). The research assistants are nurses that have successfully completed a training session on the ivWatch device and research study. The research assistants may include members of the vascular access (VAT) and perioperative (PERIOP) teams as well as the quality outcome manager. An ivWatch employee will instruct the nurses on receptacle placement and operation of the device. A document describing the placement protocol (Appendix A) will be provided if there are questions about the protocol during the study. The final role listed in Table 2 are the nurses who perform the normal care for the patient but have no specialized training for the research study. These nurses perform their normal care for the patient and are only expected to press the IV Check button on the ivWatch patient monitor after each IV site assessment.

Table 2. The three roles for the clinical study.

Role	Description	Responsibilities
Investigator	Darcy Doellman*, Sylvia Rineair*, Candice Fletcher Overly*, Neil Johnson *Investigators may also perform duties of research assistant and nurses, if applicable.	• Pediatric patient recruitment • Informed consent • Case report form review and signoff • Study oversight
Research Assistant	A CCHMC nurse that has successfully completed the training on the ivWatch device and research protocol. Examples would include nursing supervisors, Vascular Access Team, and investigators.	• Pediatric patient recruitment • IV and sensor placement • IV termination procedures • Case report form entries • Photographs • Equipment check in/out • Informed consent
Nurse	A CCHMC nurse who is directly responsible for a patient's care and typically performs PIV site placement and assessments.	• Normal patient care • IV Site assessments • Pressing IV Check button after assessments • Notify research personnel of an infiltration or when IV therapy complete

A sponsor representative will be available during the course of the study. The representative will work closely with investigators to assist in study oversight, data verification, device inventory, and data management.

Subject Recruitment

Pediatric patients at CCHMC will be recruited to participate in the study. The study will enroll newborns (weighing more than 2.5 kg) through adults (less than 18 years old) with anticipated continuous infusions of at least 24 hours. Vascular access team members will identify potential patients requiring IV placement for infusions lasting 24 hours or greater. If the patient meets the

inclusion criteria then an investigator will speak with the patient and/or legal guardian to assess interest in participating in the study.

Informed Consent Process and Preliminary Information

The pre-study procedure is listed in detail in Table 3. Once a potential pediatric patient is identified, an investigator will discuss the study and review the informed consent document according to CCHMC protocols. The investigator will discuss the main points of the study and the patient's rights, as described in the consent form, using age appropriate language. The patient, parent, or legal guardian has the right to immediately stop the study at any time for any reason.

Table 3. Procedure and checklist for preliminary information and consent process.

Step	Person	Status	Task
Preliminary Information and Consent Process			
1.	**Investigator or Research Personnel**		Patient is identified as potential study participant.
2.	**Patient**		Patient, parent, or legal guardian indicates interest in study.
3.	**Investigator or Research Personnel**		Perform the informed consent/assent process according to CCHMC protocols.
4.	**Research Assistant**		Record preliminary information in Section 1, 2, and 3 of the Case Report Form.
5.	**Research Assistant**		Record general patient information in Section 4 of the Case Report Form.
6.	**Research Assistant**		Record body measurements in Section 5 of Case Report Form. This information can be measured or transcribed from the patient record, if applicable.
7.	**Research Assistant**		Record skin pigmentation in Section 6 of Case Report Form.
8.	**Research Assistant**		Checkout ivWatch patient monitor, sensor cable, and sterile receptacle. Record identification information in checkout form. Check date / time and battery status of patient monitor and clean the ivWatch patient monitor and sensor cable with disinfectant wipes prior to starting the study. ☐ ivWatch Patient Monitor ☐ ivWatch 400 Sensor Cable ☐ ivWatch 400 Receptacle ☐ ivWatch Custom Occlusive Dressing ☐ Study camera

Case Report Forms (CRFs) designed specifically for this study will be completed. An example of the case report form is included in Case Report Forms section of this document (Page 31). The case report form number and study start date are completed in Section of 1 of the CRF.

Checkboxes for the inclusion and exclusion criteria are included in Sections 2 and 3 of the CRF. The list of study exclusion criteria is included in Table 4. The nurse, registered nurse, or investigator may use his/her professional judgment to exclude a subject for reasons not included in this list. General patient information such as gender and age are included in Section 4 of the CRF. Specific patient attributes such as weight, height, forearm circumference, arm length, and skin pigmentation are included in Sections 5 and 6 of the CRF.

Table 4. List of study exclusion criteria.

1.	Severe skin integrity issues such as severe eczema, burns, epidermolysis bullosa, rash, hives
2.	Severe scarring of tissue (excessive IV use)
3.	Tattoo in area of PIV site
4.	IV site located in antecubital fossa

Once the pre-study information is complete, the study equipment will be checked out from a secure location. The equipment includes the ivWatch patient monitor, sensor cable, custom dressing, and sterile receptacle as well as the study camera. A checkout sheet will be used to track the device inventory during the course of the study.

Data Collection

The data collection consists of three processes: (1) site preparation, (2) IV site monitoring, and (3) study completion.

Site Preparation

The IV site preparation will be performed according to the existing hospital procedures. The location of the IV site is selected using the existing hospital procedures, the placement is not dictated by this research protocol. The research assistant will record details of the IV site in Section 7 of the case report form. Details include the side and site of the IV, information about the catheter, IV site analgesia (if any), site immobilization such as an armboard or IV house, and whether the IV was placed using ultrasound guidance. If the catheter was placed with ultrasound, the depth of catheter will be recorded (distance from surface of skin to the tip of catheter).

After placing the IV catheter according to hospital procedures, the nurse places the ivWatch receptacle next to the catheter according to the ivWatch placement protocol (Appendix A). Care should be taken to avoid placing the receptacle over an area of flexion or a large vein. Occlusive dressings are placed over the site and cable management of the IV tubing and ivWatch sensor cable is performed as defined in the instructions for use.

The ivWatch sensor is connected to the ivWatch patient monitor and the research assistant starts monitoring according to the instructions listed in the ivWatch Model 400 User Manual. The infusion is started according to the prescribed infusion therapy. Preferably, the infusion would be started after ivWatch starts monitoring although this is not a critical requirement and is left to the discretion of the clinician. The research assistant records the ivWatch patient monitor serial number, the sensor cable lot number, and receptacle lot number in Section 8 of the case report form. The date and time that ivWatch monitoring was started will be recorded in Section 9 of the case report form. The date and time displayed on the ivWatch patient monitor should be used.

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A photo card with identification information (CRF number and photo ID) will be placed next to the site. The research assistant will capture a photograph using a camera provided by the sponsor including both the IV site and the photo card. The receptacle and catheter should be visible in the photograph as illustrated in Section 10 of the case report form. This photograph will be used to measure the separation between the catheter tip and the ivWatch sensor in a post study analysis. The time of the photograph is also recorded in Section 10 of the case report form.

Table 5. Procedure and checklist for data collection.

Site Preparation			
1.	**Nurse**		Place catheter at desired location according to CCHMC protocols.
2.	**Research Assistant**		Dress the IV site and place the ivWatch sensor and receptacle according to the procedure outlined in the research protocol. Route IV tubing and sensor cable to IV pole following existing hospital procedures.
3.	**Nurse**		Start the infusion.
4.	**Research Assistant**		Start monitoring of the site following the instructions listed in the ivWatch Model 400 User Manual.
5.	**Research Assistant**		Record information of the peripheral IV site in Section 7 of the Case Report Form.
6.	**Research Assistant**		Record ivWatch device information in Section 8 of the Case Report Form. Any additional receptacles used later in the study should be recorded here (if any).
7.	**Research Assistant**		Record the date and time monitoring began in Section 9 of the Case Report Form. Use the date and time displayed on the ivWatch patient monitor.
8.	**Research Assistant**		Place Section 10 photo ID card next to site. Capture photograph of dressed site (the catheter and ivWatch receptacle should be visible in the photograph). Record photograph time in Section 10 of the Case Report Form. Dispose of photo ID card.
9.	**Research Assistant**		Record information about the infusion in the first row of Section 11 of the Case Report Form. This can be transcribed from the medical administration record at a later point in time.
During IV Therapy			
10.	**Nurse**		Press the IV Check button ☑ on the ivWatch patient monitor after each assessment of the IV site.
11.	**Research Assistant**		Record any changes to the infusion during the course of IV therapy in Section 11 of the Case Report Form. This can be transcribed from the medical administration record.
12.	**Research Assistant**		If the patient is in the alarming group and the device issues a red infiltration notification, the nurse should contact the research assistant to perform an assessment. • If no infiltration is evident, the ivWatch device should be reset. The research assistant should do a second assessment approximately 30 minutes after resetting the device.
13.	**Research Assistant**		If an infiltration or other complication associated with the PIV is detected, stop infusion and continue with **Termination of IV Therapy** section below.

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Termination of IV Therapy			
14.	**Research Assistant**		Stop ivWatch monitoring following the ivWatch Model 400 User Manual. Record date and time in Section 12 of Case Report Form.
15.	**Nurse**		Remove any bandages covering the ivWatch sensor and catheter.
16.	**Research Assistant**		Record details about the IV therapy termination including reason and final site assessment in Section 13 of the Case Report Form.
17.	**Nurse**		If no infiltration is evident, perform final assessment of IV site.
18.	**Nurse**		Remove ivWatch sensor and catheter from the site. Use alcohol wipe or hospital product remover to help peel the ivWatch sensor from the skin.
19.	**Research Assistant**		Place Section 14 photo ID card next to site. Capture photograph of bare site. Record photograph time in Section 16 of the Case Report Form. Dispose of photo ID card.
20.	**Nurse**		Apply adhesive bandage to site consistent with existing CCHMC protocols.
21.	**Nurse**		If infiltration or extravasation was detected, follow hospital procedures for treatment.
Case Study Completion			
22.	**Research Assistant**		Provide contact information should the patient (or parent/legal representative) have questions after leaving.
23.	**Research Assistant**		Complete Sections 15 (Miscellaneous Notes) and Section 16 (Adverse Events) of the Case Report Form.
24.	**Research Assistant**		Remove tape and clean ivWatch sensor with hospital-grade disinfectant wipes. Return ivWatch patient monitor and sensor cable and complete the equipment check-in sheet.
25.	**Research Assistant**		Return completed Case Report Form to investigator.
26.	**Investigator**		Review entries in Case Report Form to ensure that the form is both complete and correct. Complete Section 17 of the Case Report Form.

IV Site Monitoring

The ivWatch patient monitor will collect data throughout the IV therapy. The monitor will collect data even when the IV therapy is temporarily stopped via a heparin or saline locked catheter. Nurses are asked to press the IV Check button on the ivWatch patient monitor after each assessment of the IV site. The intent of this instruction is to demonstrate the performance of this feature in the IPM software and strict compliance is not required. The *IV Check* button is illustrated in Figure 4.

Changes to the infusion will be recorded in Section 11 of the case report form. Changes to the rate, infusate, or medicine should be recorded in this section. Temporary suspension of IV therapy such as a heparin-locked or saline-locked catheter should also be recorded. This information can be transcribed from the medical administration record.

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For subjects in the pilot and non-alarming groups, the ivWatch patient monitor will only issue audible notifications if the acquired signals appear erroneous. A sensor monitoring error is issued when (1) the sensor is disconnected from either the patient or the ivWatch patient monitor, or (2) large, rapid changes in the ambient light level are detected. This error corrects itself once the signals return to normal levels, for example, the sensor is re-attached to the patient. It typically takes approximately 6 seconds after the signal returns to normal levels to dismiss the sensor monitoring error. The device will dismiss errors automatically should the signals return to appropriate levels and does not require a manual reset of the device by the clinician.

For subjects in the alarming group, the infiltration notifications will be enabled. The ivWatch device will issue yellow and red notifications should the measured signal suggest an IV site infiltration may have occurred. As described in the instructions for use, the yellow infiltration notification is an early warning indicating that the signal levels at the site are starting to appear like an infiltration is occurring. Yellow infiltration notifications can be automatically dismissed by the ivWatch device if the signal returns to normal levels. A red infiltration state indicates that the signal conditions indicate a greater probability that an infiltration has occurred. Once a red notification is issued, the ivWatch monitor is locked in the red state until a clinician can assess the site.

If a red infiltration notification is issued, the research assistant should make an assessment of the IV site. If an infiltration is confirmed by the research assistant, the bedside nurse should be immediately notified. If they concur, the IV therapy should be stopped and the clinicians should follow the standard CCHMC protocols for handling infiltration and extravasation events. If no infiltration is evident, the research assistant should restart the ivWatch device. The research assistant should perform an additional assessment 30 minutes after such a notification. The bedside RN will continue to perform his/her normal IV site assessments.

If an infiltration or other complication associated with the PIV site is detected, regardless of how it was detected (bedside RN, research assistant, ivWatch device), the IV therapy will be stopped and the procedures defined by CCHMC will be followed.

Study Completion

The study will end when the PIV therapy is complete or when the PIV needs to be replaced due to either a complication (e.g. infiltration, phlebitis, occlusion) or the site reached the maximum permissible dwell time defined by the hospital. When PIV therapy is completed, the ivWatch patient monitor will be stopped and the time and date will be recorded in Section 12 of the case report form. Details about the termination of the IV site will be recorded in Section 13 of the case report form. If appropriate, an assessment will be performed to confirm that the catheter was in the vein at the end of IV therapy. Details on the final assessment of the site will also be recorded including whether the site is cool to the touch or if blanching of the skin or swelling of the site is evident. If swelling is apparent, the length of the swelling is measured in centimeters. If the IV therapy was terminated due to a complication, such as infiltration, extravasation, or phlebitis, the standard hospital procedures should be followed for treatment.

The sensor and catheter are removed from the site. If necessary, alcohol wipes or the hospital's product remover should be used to gently de-adhere the sensor from the patient's skin. A final picture of the site should be captured to record the appearance of the skin at the conclusion of the study. The corresponding photo ID card should be placed next to the site. A photograph

should be captured of both the bare site and the photo ID card. The time of the photo should be recorded in section 14 of the case report form. The nurse or research assistant should then apply an adhesive bandage to the site consistent with existing CCHMC protocols.

Once the study is complete, the Sections 15 (Miscellaneous Notes) and 16 (Adverse Events) of the case report form should be completed. A study related adverse event is defined as unintended harm to the patient likely caused by either the ivWatch Model 400 device or research protocol. Examples of events that would typically be considered adverse events are included in Table 6. Local allergic reactions, thermal burns, skin tearing or other disruptions to skin integrity are considered adverse events. Temporary redness at the site after removing the receptacle or common IV site complications are typically not considered adverse events. The items in Table 6 are meant to exemplary but ultimately the clinician should use his/her professional judgment to discern whether harm was due to the ivWatch Model 400 device or the research protocol.

Table 6. Potential study related adverse event examples.

Adverse Events	Not Adverse Events
• Allergic reaction of skin at receptacle	• Temporary redness at site after receptacle removal
• Thermal burns associated with sensor	• Common IV site complications (infiltration, phlebitis, thrombosis, embolism)
• Tearing of skin due to receptacle adhesive	• Cardiopulmonary complications (pulmonary embolism)
• Strangulation or tripping by ivWatch sensor	• Events related to the reason for the patient's hospitalization

The research assistant is responsible for cleaning the ivWatch Model 400 equipment. This includes removing tape connecting the IV tubing to the ivWatch sensor, disposing the used IV tubing and ivWatch receptacle, and cleaning the ivWatch sensor and monitor with hospital-grade disinfectant wipes. The IPM and sensor cable will be returned to the secure location designated by the principal investigator and the research assistant will complete the check in sheet to maintain an accounting of the ivWatch device inventory. The case report form should be returned to an investigator.

An investigator will perform a final check of the case report form including any final transcription from the patient record or medical administration record. Once complete, the investigator will authorize the form by signing Section 19 of the case report form.

Data Analysis

Specific analyses to be performed with the data are included below. The study group used in each analysis are included in parentheses.

- **Time Difference between Detections (Non-Alarming Group)**
  - The difference in time to detection between the nurse and the ivWatch device is measured from the non-alarming group. This information tells how much earlier the infiltration could have been detected by ivWatch compared to the nursing standard. This metric is measured using the patients in the non-alarming group

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since an infiltration notification by the ivWatch device could bias the nurse's diagnosis.

- **Infiltration Sensitivity (Non-Alarming Group)**
  - The infiltration sensitivity is defined as the percentage of the nurse-confirmed infiltrations that are detected by the ivWatch device before the nurse's diagnosis. This metric is measured using the patients in the non-alarming group since an infiltration notification by the ivWatch device could bias the nurse's diagnosis.
- **Notification Rate (Alarming Group)**
  - The notification rate is how often the ivWatch device issues infiltration notifications in a certain amount of time, typically reported in units of notifications per day. The notification rate is a combination of both false and true notifications – the false notification rate cannot be accurately determined with no gold standard available for comparison. This metric is measured using the patients in the alarming group since the number of notifications could potentially depend on how quickly nurses reset the device.

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

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

Safety Considerations

Long Term PIV Placement

The study design is considered to have minimal risk to the pediatric subjects participating in this study. All subjects will be receiving PIV therapy according to a physician's order. In this protocol, the only change to standard care of the patient is the placement of the ivWatch receptacle next to the PIV site. The receptacle and occlusive dressing are sterilized to minimize the risk for infection. The adhesives and plastics are biocompatible and no cases of significant skin irritation or disruption to skin integrity due to the ivWatch components have been reported. The sensor/receptacle do not visually block the PIV site such that clinicians may still assess the site using the hospital protocols. Observations by the ivWatch device are not intended to alter or replace observations by hospital staff.

Common complications of PIV placement include but are not limited to phlebitis, infiltration, extravasation, and emboli. Since the PIV is required, these risks would be present with or without participation in this study. Hospital procedures will be followed to minimize these risks and standard care will be used to evaluate and mitigate these risks.

The ivWatch Technology

The ivWatch technology has been consistently determined to be a non-significant risk as determined by the FDA. A letter from the FDA indicating this designation for the technology is

included in Non-Significant Risk (NSR) Classification section of this protocol (Page 40). 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. Earlier prototypes have been evaluated in previous clinical studies with IRB approval. A list of these studies is included in Table 7. The materials used for the receptacle and sensor have passed biocompatibility testing. Receptacles and dressings which have direct contact with the skin are individually packaged and sterilized. The amount of LED light emitted by the sensor into the subject's skin is significantly less than the maximum permissible ocular and skin exposures published in 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 ivWatch Model 400 has obtained 510(k) clearance for adult usage and this clinical study will investigate the performance of the device in a pediatric population.

Table 7. Previous 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: 00008513
The Signal Variation of Normal Tissue	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00008218
The Effect of Catheter Depth	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00008254
The Effect of Infiltration Rate	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00008941
Long Term Adhesion of the ivWatch Receptacle	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00008891
Device Validation for Non-Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00009175
Device Validation for Infiltrated Tissues	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00009285
The Effect of Sensor-to-Catheter Distance	ivWatch, LLC	ivWatch, LLC	Chesapeake IRB: 00010217

Follow-Up

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

Data Management and Statistics

Data Management

Each patient participating in the study is assigned a unique case report form number. This number is incremented sequentially for each pediatric patient participating in the study. For example, the first patient of the clinical study will have forms coded as CRF1 and the fourth patient will have a case report form coded CRF4. The site investigators will be responsible for determining the appropriate case report form number for newly enrolled pediatric patients. The record tying the patient with the case report form will be securely stored at CCHMC.

The case report form was designed to ensure values are recorded consistently throughout the study. This CRF design included using checkboxes to select categorical data. For example, rather than providing a simple text entry, the case report form provides a checklist of the likely IV site analgesics for the research assistant to select. For some information, particularly the infusion and medication information, a checklist of all potential combinations was not practical. This information is transcribed from the medical record and should be easily interpreted by a clinician. The purpose of the infusion and medication characteristics is to understand cases with anomalous data. Since a thorough statistical analysis of the infusion and medication data will not be performed, coding of this information is not deemed necessary for the purposes of this study.

Once a case study is complete, the electronic patient monitor data and photograph images will be transferred to a directory on a laptop. This directory is actively and securely synced to a repository at the ivWatch facilities in Williamsburg, VA, as illustrated in Figure 5. Only authorized users can access the computer or repository. The paper case report and informed consent forms will be scanned into PDF format and stored in this directory.

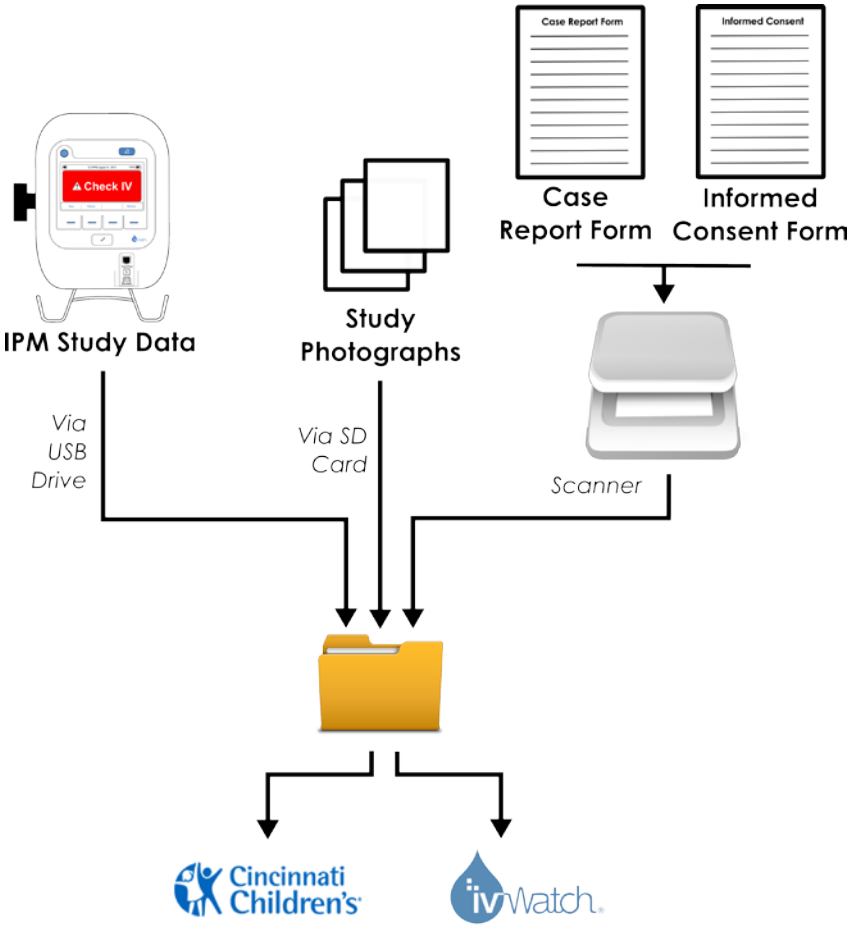

Figure 5. Data management for clinical study.

At the conclusion of the study, all source data (paper forms and electronic data) will be stored at CCHMC. Electronic data will be copied from the repository into a secure medium, such as a password protected CD or USB drive, which will be kept at CCHMC. As recommended by the FDA, storage of source data at the investigation site is important for ensuring data authenticity. The sponsor will receive a copy of this source data.

The sponsor will combine all data collected (paper and electronic) in an electronic database for internal data analysis. Filemaker Pro Advanced 13 and Filemaker Server 13 are used for this electronic database. 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. Requests for data clarification will be sent to the study investigator. All additions and changes to fields in the clinical database will automatically log the date, time, user name, field identifier, prior value, and new value. If a field was edited, a reason for the change will be recorded. No manual edits or deletions to this audit log will be made. Users will not be permitted to delete records. Data will be validated during the data entry process. After validation is complete, the database will be available to only authorized users.

Statistical Analysis

Statistical Power Analysis

Monte Carlo simulations were performed to estimate the statistical power for different numbers of detected infiltrations. To estimate the time of detection by the ivWatch device, a statistical model was used based on the results of a 140 infiltration study of adult volunteers. Although the adult volunteers had larger extremities, the time to detection is expected to be similar between adults and pediatrics. Since the time to detection by ivWatch depends linearly with the infiltration rate, infusion rates from the Phase I pilot study were randomly sampled using bootstrapping techniques (random sample with replacement). For the time of nurse detection, the model assumed the nurse had a uniform probability of detecting the infiltration within the first two hours of the infiltration. This is believed to be a conservative assumption because the nurse detected the infiltration on average 20 hours after the ivWatch device in the Phase I pilot study. One hundred thousand simulations were performed for each number of infiltrations. In each iteration, the randomly determined ivWatch and nurse detection times were evaluated using an unpaired, one-tailed, two sample t-test with a 5% significance level. The statistical power was calculated as the percentage of the 100,000 simulations that rejected the null hypothesis, where the null hypothesis was defined as having no difference between the nurse and ivWatch detection times. The results of this analysis are shown in Table 8.

Table 8. Statistical power analysis for detecting a statistically significant difference between ivWatch and nurse time of detection.

Number of Infiltrations	Statistical Power (%)
3	63.2
4	82.5
5	**90.8**
6	94.4
7	96.0
8	97.1

Five infiltrations was selected because (1) five provides a sufficient statistical power of 91% for detecting a difference between the ivWatch device and nurse time to detection and (2) it is a reasonable number of infiltrations to capture in 150 subjects. In the Phase I pilot study, five nurse-confirmed infiltrations were recorded from the 127 case studies. The MATLAB code for generating the statistical power estimates is included in Figure 6.

```
clear variables;
close all;
clc;

% Assume that the ivWatch device detects at a volume of 10 mL. This is a
% worst case assumption as infiltrations in adults were generally detected
% with less than 5 mL infiltrated
ivw_volume_detect = 10; %mL

% Load the recorded flow rates from the pilot study
```


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```
load('flow_rates.mat');

fprintf(1,'N\tStatPow\r');

% Perform simulations when 3, 4, 5, 6, 7, and 8 infiltrations are detected

for N = 3:8;

    % Simluate 100,000 studies where N infiltrations are detected
    for i=1:100000

        % Randomly sample the flow rates in the CCHMC pilot study
        rs_flow_rates = datasample(flow_rates, N);

        % Estimate the time to alarm based on empirical relationships from
        % adult studies with the ivWatch device
        ivw_detect_volume = 0.02481*rs_flow_rates+1.871 + 1.739*randn(size(rs_flow_rates));
        ivw_times = (ivw_detect_volume)./rs_flow_rates;
        ivw_times(ivw_times<2/60)=2/60;

        % Assume the nurse has a uniformly distributed probability of
        % detecting the infiltration within the first 2 hours. Recall, that
        % the average difference in time to detection was 20 hours for the
        % CCHMC pilot study, so this assumes better performance from the
        % nurse relative to what was seen in the pilot study (i.e. it is a
        % conservative estimate).
        nurse_times = 2*rand(N,1);

        % Calculate t-test on times (h=1 if reject null hypothesis, h=0 if can
        % not reject null hypothesis)
        h(i) = ttest2(ivw_times, nurse_times,'tail','left');

    end

    % Print the results of the simulation to the console
    fprintf(1,'%f\t%f\r', N, sum(h)/length(h) );
end
```

Figure 6. The MATLAB code used to generate the statistical power estimates as a function of the number of nurse-confirmed infiltrations.

Post Study Analysis

The statistical analyses to be performed at the conclusion of the study are summarized in Table 9. The mean difference in detection time between the ivWatch device and nurse will be calculated and the 95% confidence interval for this mean will be estimated using a Student's t-distribution. The infiltration sensitivity (how many nurse-confirmed infiltrations were detected by the ivWatch device) will be calculated and the 95% confidence interval will be estimated using the Clopper-Pearson method for calculating confidence intervals for binomial proportions. The notification rate will be calculated and the confidence interval will be calculated using a negative binomial statistical model.

Table 9. The post study analyses.

Performance Metric	Analysis
Time Difference	Mean and 95% confidence interval from Student's t-distribution
Infiltration Sensitivity	Binomial proportions with 95% confidence interval from Clopper-Pearson method.

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Notification Rate	Negative binomial model for rate and 95% confidence intervals

Quality Assurance

As the research sponsor, ivWatch, LLC will continually monitor the research studies to ensure subject safety, protocol compliance, and data validity.

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 and research assistants) will have the proper training for conducting clinical trials prior to the start of the study. The subject screening will be performed by an investigator or research assistant familiar with the study.

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 Model 400 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 a database are password protected and restricted to authorized users. Any changes to the database are tracked. The case report forms do not contain patient identifiers. All paper health history forms will be stored in a locked office.

Expected Outcomes of the Study

The expected outcome of this study is a formal assessment of the ivWatch Model 400 for monitoring pediatric PIV sites. This assessment will include whether the ivWatch device can detect infiltrations prior to a nurse's diagnosis and, if so, measure how much earlier the ivWatch detected infiltrations prior to the nursing standard of care. The assessment also includes additional diagnostic measures of (1) the device sensitivity, defined as the percentage of nurse-confirmed infiltrations that were detected by the ivWatch device, and (2) the notification rate, defined as the number yellow or red notifications issued in a given period of time. The results of this study will be important for future regulatory considerations and identifying future product improvements.

Dissemination of Results

Gary Warren, CEO of 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 Infusing Nurses Society and Association for Vascular Access.

Duration of the Project

Each study will last until the PIV infusion therapy is complete. The entire study is expected to require approximately 5-9 months to complete.

Problems Anticipated

Project timing and budgeting difficulties are not anticipated for this research project. First, the study consists approximately 340 subjects (310 accepted case studies). These subjects will be patients at CCHMC. ivWatch is confident that the necessary data can be collected from the 340 subjects within nine months. Second, the budget for this project is funded internally by ivWatch, LLC. ivWatch will pay for any costs as provided in the Clinical Trial Agreement and any amendments that may occur during the course of this research project.

Ethics

ivWatch, LLC and CCHMC will follow ethical and regulatory guidelines while conducting this study. The investigators will not proceed with the study until informed consent and informed assent (if applicable) has been given. 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.

Informed Consent Forms

Please see the attached informed consent form.

Case Report Forms

IVW-CLR-CS09-400-CRF
IRB #: XXXXXXX

CRF _____

Case Report Form

1. General Study Information	
Case Report Form #: _____	**Study Start Date** (yyyy/mm/dd): _____

2. Inclusion Criteria

☐ Signed consent and/or assent ☐ Newborn to 17 years of age ☐ Weight > 2.5 kg

3. Exclusion Criteria

The patient should be excluded from the study if the answer is yes for any of the following items:

	Yes	No
Severe skin integrity issues such as severe eczema, burns, epidermolysis bullosa, rash hives	☐	☐
Severe scarring of tissue at IV site	☐	☐
Tattoo in area of PIV site	☐	☐
IV site to be monitored in antecubital fossa	☐	☐
Other	☐	☐

If other, please specify: _____

4. General Patient Information

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

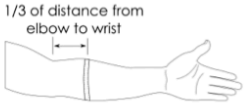
5. Body Measurements

Weight: _____ kg

Height or Length: _____ cm

Forearm Circumference: _____ cm

Arm Length: *(axilla to tip of longest finger)* _____ cm



6. Skin Pigmentation

☐ Light ☐ Medium ☐ Dark

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IRB #: XXXXXXX

CRF _____

Case Report Form

7. Peripheral IV Site	
Side of Patient *(Select One)*	☐ Left ☐ Right
Location on Patient *(Select One)*	☐ Hand ☐ Forearm ☐ Foot ☐ Scalp
Catheter Gauge *(Select One)*	☐ 20 ☐ 22 ☐ 24 ☐ Not Sure ☐ Other If other, please specify: _____
Catheter Length *(Select One)*	☐ 0.56 in ☐ 0.75 in ☐ 1.00 in ☐ 1.25 in ☐ Not Sure ☐ Other If other, please specify with units: _____
Immobilization Options *(Select One)*	☐ Armboard ☐ IV House ☐ Hubguard ☐ None
Ultrasound Guidance *(Select One)*	☐ Yes ☐ No If yes, please record depth of vessel: _____ mm
IV Site Analgesia *(Select All That Apply)*	☐ None ☐ Vapocoolant Spray ☐ Subcutaneous buffered lidocaine ☐ Buzzy Bee ☐ Topical lidocaine ☐ Other If other, please specify: _____

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IRB #: XXXXXXX

CRF _____

Case Report Form

8. ivWatch Device and Materials

ivWatch Patient Monitor Serial Number:	ivWatch Sensor Cable Lot Number: *(white label on sensor cable)*
	–

Please complete a row for each receptacle used. If more space is needed, please use the miscellaneous notes section of the case report form.

	Date (YYYY/MM/DD)	Time (HH:MM)	Lot Number
1			–
2			–
3			–
4			–

9. Start of ivWatch Monitoring

Please use the time and date displayed on the ivWatch Patient Monitor.

Monitor Start Date (yyyy/mm/dd) _____

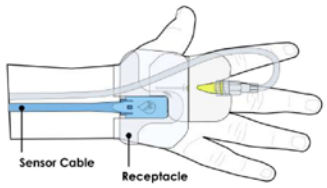
Monitor Start Time (HH:MM) _____

10. IV Site Photograph at Start of Case Study

Place Section 10 Photo Card near site.

The catheter and receptacle should be visible in the photograph, as illustrated to the right.

Photo Time (HH:MM) _____



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IVW-CLR-CS09-400-CRF
IRB #: XXXXXXX

CRF _____

Case Report Form

11. Infusion Characteristics

Complete this table describing the infusion characteristics. Each row corresponds to a change in the infusion therapy including rate and medication changes. If no medication is given, please write None in the medication field. If the catheter is hep-lock or saline-locked, please record an IV Rate of 0 mL/hr. Do not use ditto marks (").

Date *YYYY/MM/DD*	**Time** *HH:MM*	**Infusate**	**IV Rate** *mL/hr*	**Medication**

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IVW-CLR-CS09-400-CRF
IRB #: XXXXXXX

CRF _____

Case Report Form

Date YYYY/MM/DD	Time HH:MM	Infusate	IV Rate mL/hr	Medication

IVW-CLR-CS09-400-CRF
IRB #: XXXXXXX

CRF _____

Case Report Form

12. Stop ivWatch Monitoring	
Monitoring Stop Date (yyyy/mm/dd) _____	**Monitoring Stop Time** (HH:MM) _____

13. Termination of IV Therapy	
Reason for Termination *(Select One)*	☐ Therapy Complete ☐ Infiltration or Extravasation ☐ Phlebitis ☐ Occlusion ☐ Site Infection ☐ Other If other, please specify: _____
Edematous Patient *(Select One)*	☐ Yes ☐ No
Catheter Assessment *(Select One)*	Catheter is: ☐ In Vein ☐ Out of Vein ☐ Not Performed
Skin Feels Cool at Site *(Select One)*	☐ Yes ☐ No
Skin Blanching at Site *(Select One)*	☐ Yes ☐ No
Swelling at IV Site *(Select One)*	☐ Yes ☐ No If yes, please specify the length of swelling: _____ cm
Infiltration or Extravasation	Did an infiltration or extravasation occur? ☐ Yes ☐ No If yes, please record the following details from the CCHMC Extravasation Grading Scale (see attached): Relative Swelling (%) ☐ Medication Component (R,Y,G,F,U,N) ☐

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14. Bare Site Photograph After Study Complete

Place Section 14 Photo Card near site.

Photo Time
(HH:MM PM) _____

15. Miscellaneous Notes

Are there any additional comments related to the case study? ☐ Yes ☐ No
If yes, please include the comments here:

16. Adverse Events

Did the patient experience any unexpected harm associated with the ivWatch Model 400 device or the research protocol? ☐ Yes ☐ No

If yes, please explain:

17. 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

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IRB #: XXXXXXX

CRF _____

May 23, 2011
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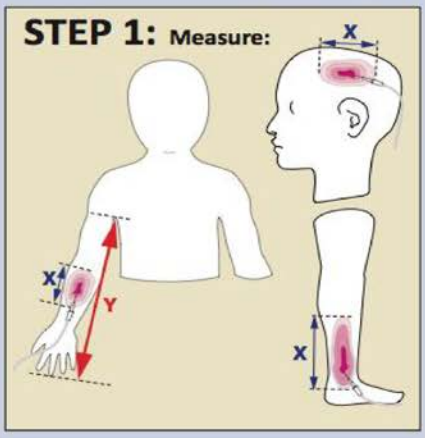
Peripheral Intravenous (PIV) Extravasation Grading Scale

Volume Component

STEP 1: Measure:



STEP 2: Calculate

$$\left(\frac{X}{Y}\right) \cdot 100 = \square\ \%$$

Notes:

- Define edges of swelling by palpation/visual observation
- For all extravasations, including scalp, leg, chest, always use the same Y measurement (Use either right or left arm)
  NEVER use a leg or other measurement for "Y"
  X = maximum dimension (length or width) of swelling
  Y = tip of longest finger to anterior/inferior skin fold of axilla with arm as straight as possible
- For rare patients with limb malformations, or contractures use age appropriate CCHMC table for the "Y" measurement. DO NOT use this table for patients with normal arms.

STEP 3: Medication Component

Peripheral Venous* Infusion Risk

Red (Higher Risk)	Yellow (Intermediate Risk)	Green (Lower Risk)
Acyclovir	Acetazolamide	
Caffeine Citrate	Alkanized	
Calcium	Amikacin	
Dextrose > 10%	Amphotericin B (conventional)	
Doxycycline	Arginine	
Mannitol 20% & 25%	Ciprofloxacin	
Promethazine	Dextrose 5% to 10%	
Potassium	Erythromycin	
Sodium bicarbonate	Gatifloxacin	
Sodium chloride > 3%	Levofloxacin	
TPN > 10% actual	Midazolam	
Vasopressors such as Dopamine	Morphine	
Chemotherapy Drugs	Ondansetron	
	Nafcillin	
	Non-Ionic Radiology Contrast	
	Phenobarbital	
	Phenytoin	
	Potassium > 40 mEq/L	
	TPN 10% actual	
	Vancomycin	

NOTE: No peripheral infusions of a vesicant (see extravasation, pain of normal saline, may result in serious harm including compartment syndrome, causing ischemia and loss of tissue or permanent loss of limb function.

* Peripheral Venous Access is defined as any Venous Access Device where tip does not reside in the Right Atrium, Superior / Inferior Vena Cava, or the Brachiocephalic Vein

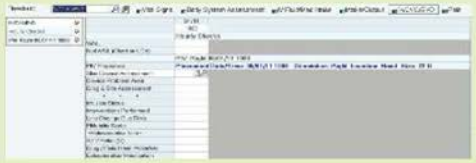
Notes:

- Medication Component means medications administered through the IV during the previous two hours, or since the last routine normal IV site check, whichever is longer.
- Refer to current Red/Yellow/Green listing available on Centerlink.

MEDICATION CODING

R = medication on RED list
Y = medication on YELLOW list
G = medication on GREEN list
F = Fluids only (no medications or potassium)
U = medication Unlisted
N = medication not listed but causing harm similar to a RED drug (this category will rarely be needed)

STEP 4: Chart immediately in all cases



Notify Vascular Access Team as soon as possible if:

Volume = >25% or RED list Drug

Vascular Access Team Pager:

736-0337

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IVW-CLR-CS09-400-CRF
IRB #: XXXXXXX

CRF _____

Peripheral Venous* Infusion Risk

This is an estimate of risk for phlebitis or local tissue injury due to extravasation.
Risk derived from available evidence, CCHMC data and CCHMC expert opinion, subject to review and change as further evidence becomes available.

This does not apply in situations of emergency medical treatment.
If a medication is not on this list, please refer to the CCHMC formulary or contact pharmacy (8-4291) for information

Red
Higher Risk

Acyclovir
Caffeine Citrate
Calcium *(all salt forms)*
Dextrose > 12.5%
Doxycycline
Mannitol 20% & 25%
Promethazine
Potassium >60 mEq/L
Sodium bicarbonate
Sodium chloride ≥ 3%
TPN > 950 mOsm/L
Vasopressors such as Dopamine

Chemotherapy Drugs

Yellow
Intermediate Risk

Acetazolamide
Allopurinol
Amikacin
Amphotericin B (conventional)
Arginine
Ciprofloxacin
Dextrose 10% to ≤12.5%
Erythromycin
Ganciclovir
Lorazepam
Midazolam
Morphine
Ondansetron
Nafcillin
Non-Ionic Radiology Contrast
Phenobarbital
Phenytoin
Potassium ≤ 60 mEq/L
TPN ≤950 mOsm/L
Vancomycin

Green
+ Lower Risk

Aminophylline
Amphotericin B Liposomal
Ampicillin
Ampicillin/Sulbactam
Cefazolin
Cefotaxime
Ceftazidime
Ceftriaxone
Cefuroxime
Clindamycin
D5LR
Dextrose < 10%
Diazepam
Fentanyl
Fosphenytoin
Furosemide
Gentamicin
Heparin
Imipenem
IVIG
Lactated Ringers
Lipids
Magnesium sulfate (bolus)
Meropenem
Methylprednisolone
Normal saline
Pentamidine
Piperacillin

Piperacillin/tazobactam
Ticarcillin
Ticarcillin/clavulanate
Tobramycin

NOTE:
No peripheral intravenous infusate is "safe". Gross extravasation, even of normal saline, may result in serious harm including compartment syndrome, causing ischemia and loss of tissue or permanent loss of limb function.

Cincinnati Children's

* Peripheral Venous Access is defined as any Venous Access Device whose tip lies outside the Right Atrium, Superior / Inferior Vena Cava, or the Brachiocephalic Veins

June 1, 2011

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Non-Significant Risk Designation

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 20 2003

Leonard W. Winchester, Jr., Ph.D.
Chief Scientist and Vice-President
CW Optics, Incorporated
905 Seaford Road
Seaford, Virginia 23696

Re: Q030041 – Optical Intravenous Infiltration Monitoring Prototype Device

Dear Dr. Winchester:

The Food and Drug Administration (FDA) has reviewed your facsimile, dated November 17, 2003, proposing clinical investigation that utilizes your Optical Intravenous Infiltration Monitoring Prototype Device. FDA has determined that your proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812, available on the internet at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=812).

An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. A NSR study is, however, subject to the abbreviated requirements described in § 812.2(b) of the IDE regulation. The abbreviated requirements stipulate that the sponsor of the investigation must label the device in accordance with § 812.5; obtain institutional review board approval of the investigation as a NSR study; ensure that each investigator obtains informed consent from each subject under the investigator's care; comply with the monitoring requirements of § 812.46; maintain records required under § 812.140(b)(4) and (5) and file the reports required under § 812.150(b)(1) through (3) and (5) through (10); and ensure that participating investigators maintain the records required by § 812.140(a)(3)(i) and file the reports required under § 812.150(a)(1), (2), (5) and (7).

Under the abbreviated IDE requirements, a sponsor must also comply with the prohibitions against promotion and other practices as identified in § 812.7. According to this section of the regulation, the sponsor of a NSR study, investigator, or any person acting for or on behalf of the sponsor or investigator is prohibited from promoting or test marketing the investigational device until after FDA has approved the device for commercial distribution; commercializing the device by charging a price greater than that necessary to recover the cost of manufacture, research, development, and handling; unduly prolonging the investigation; and representing the investigational device as being safe or effective for the purposes for which it is being investigated.

Page 2 – Dr. Winchester

If you have any questions regarding our NSR determination or the abbreviated IDE requirements, please contact me at (301) 594-1190.

Sincerely yours,

Paul A. Williams, B.S.E.
Investigational Device Exemption Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

510(k) Clearance Letter for Use on Adults

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 19, 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,

e 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

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Investigator Signatures

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: Darcy Doellman, MSN, RN, CRNI, VA-BC

Signature: _____

Date: _____

Investigator

Name: Sylvia Rineair, MSHA, BSN, RN, VA-BC

Signature: _____

Date: _____

Investigator

Name: Candice Fletcher Overly, MSN, RN, VA-BC

Signature: _____

Date: _____

Investigator

Name: Neil Johnson, MD

Signature: _____

Date: _____

Works Cited

[1] E. M. Kagel and G. M. Rayan, "Intravenous catheter complications in the hand and forearm," *J Trauma-Injury Infection & Crit Care,* vol. 56, no. 1, pp. 123-127, Jan 2004.

[2] C. M. Rickard, J. Webster, M. C. Wallis, N. Marsh, M. R. McGrail, V. French, L. Foster, P. Gallagher, J. R. Gowardman, L. Zhang, A. McClymont and M. Whitby, "Routine versus clinically indicated replacement of peripheral intravenous catheters: a randomised controlled equivalence trial," *Lancet,* vol. 380, pp. 1066-1074, 2012.

[3] D. T. Gault, "Extravasation injuries," *Br J Plast Surgery,* vol. 46, no. 2, pp. 91-96, Mar 1993.

[4] J. Pettit, "Assessment of Infant with a Peripheral Intravenous Device," *Adv Neonatal Care,* vol. 3, no. 5, 2003.

[5] S. Phelps and R. A. Helms, "Risk factors affecting infiltration of peripheral venous lines in infants," *J Pediatr,* vol. 111, no. 3, pp. 384-389, Sep 1987.

[6] S. Masoorli, "Infusion therapy lawsuits," *J. Intravenous Nursing,* vol. 18, pp. 88-91, 1995.

[7] J. B. B. a. C. L. Jacobs, "Contrast media reactions and extravasation: Relationship to intravenous injection rates," *Radiol.,* vol. 176, pp. 411-416, 1998.

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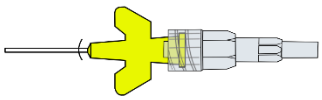
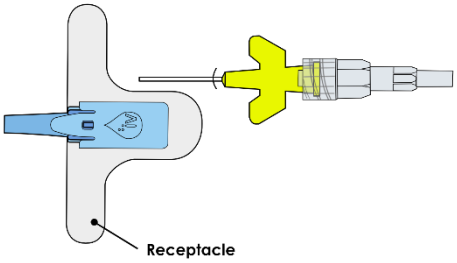
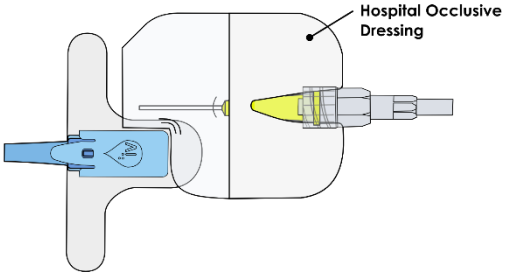
Appendix A Receptacle Placement Protocol



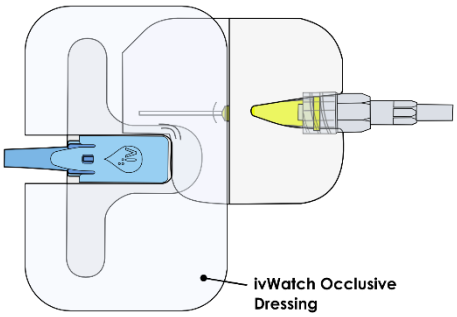
Step 1: Place the IV catheter and attach IV tubing according to hospital protocols.



Step 2: Place the ivWatch receptacle as close to catheter tip as possible (note: the ivWatch sensor cable should be inserted into the receptacle before adhering to the skin).



Step 3: Place the hospital occlusive dressing over the catheter, but not over the blue portion of the receptacle.



Step 4: Place the ivWatch occlusive dressing over the receptacle. This provides further securement to the ivWatch receptacle.

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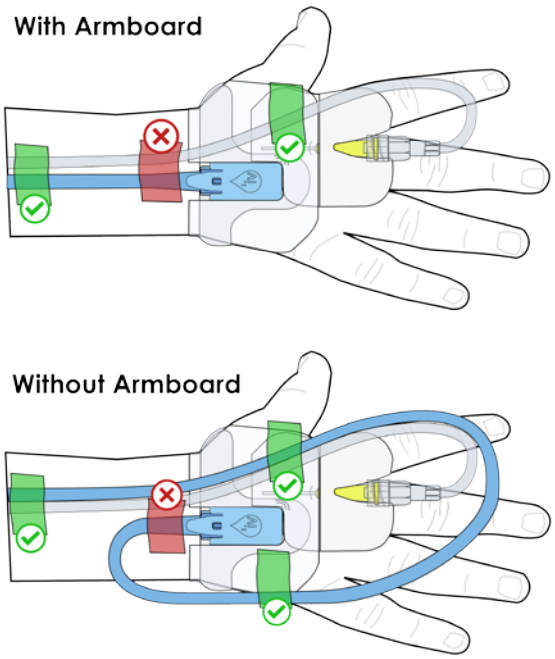

Step 5: Secure sensor cable and IV tubing consistent with hospital procedures and ivWatch instructions for use.

With an armboard, the sensor can be routed up the arm toward the body.

Without an armboard, the sensor should be routed around the hand to join the IV tubing.

Tape should not be placed directly behind the ivWatch sensor as this may lead to false notifications.

The tape and securement shown here is a suggested configuration and can be modified by the clinician based on the age and condition of the research subject.

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Appendix B Rejected Case Studies

There were 30 rejected case studies due to insufficient documentation or data, and protocol deviations. These cases are described below. All efficacy analyses were performed with the 213 accepted case studies.

Unknown Ending (22 cases)

Several cases were rejected because the case report form was not completed at the end of the study. The infiltration status of the IV was not properly assessed and documented as per the research protocol. In these cases, Section 13 of the case report form, "Termination of IV Therapy", was incomplete. The CRF numbers that were rejected for this reason are 14, 19, 24, 27, 31, 55, 77, 95, 105, 109, 116, 128, 134, 136, 139, 140, 143, 149, 151, 176, 180, and 212. All but one (CRF 212) of these subjects were in the non-alarming group.

CRF 31 was an infiltration case, but the documentation at the end of the case study is unclear. There was no measurement taken of the length or the percentage of swelling for the infiltration. Additionally, the data indicates that something unusual happened toward the end of the monitoring run. This is evidenced by discrepancies on the CRF such as the monitoring stop time is recorded at 21:25, but the end of the recorded data is 24 minutes later at 21:49. The post-study site image was taken 4 hours later, at 01:25. No notes were recorded in the miscellaneous notes section describing the differences in timing. Additionally, the sensor cable was found to be broken at the end of study.

Incomplete Data (3 cases)

Three cases were rejected because of incomplete data recorded by the ivWatch device.

For CRF 42, the sensor was placed, but the ivWatch Patient Monitor was never started. There was no clinician detected infiltration for CRF 42.

For CRF 73, only 3 hours of monitoring data were collected, where the case report form indicates 22 hours of data should have been collected. This case was a 9 month old with an infiltration of 80% swelling detected 19 hours after the ivWatch device stopped monitoring.

For CRF 145, only 3 hours of data were collected; however, the case report form indicates 21 hours of data should have been collected. There was no clinician detected infiltration for CRF 145.

The ivWatch device may have intentionally been turned off, or a few other scenarios could have caused the ivWatch device to stop collecting data. The ivWatch device may have not been plugged in, and its back-up battery died. Or, a software crash on the ivWatch device could have caused it to stop monitoring. Since there is currently no log file saved on the ivWatch device indicating a history of events, we can only speculate why monitoring stopped. One important clue is the number of readings saved in the monitoring run. If the number of readings is divisible by 16, it is likely the device stopped monitoring without user intervention because the battery died or there was a software crash. This is because data is saved in a buffer of 16 readings, unless monitoring is stopped by the user, in which case the current number of readings (some number between 1 and 16) in the buffer is saved.

The number of readings in the data file for CRF 145 is not divisible by 16, therefore the monitoring run was most likely stopped by a user.

The number of readings in the data file for CRF 73 is divisible by 16. This means there is a 1/16 chance the user stopped the monitoring run intentionally. Or, the device could have shut down because of a dead battery or software crash.

Insufficient Monitoring Data (2 cases)

According to the study protocol, subjects with an anticipated catheter dwell time of at least 24 hours were included in the study. In the case of CRF 38, the patient ripped out the IV after only 90 minutes of monitoring, and the case study was stopped. For CRF 181, the surgeon requested removal of the ivWatch device after only 30 minutes of monitoring. The investigators decided there was insufficient data collected on these 2 cases, and therefore they were rejected.

Sensor Not Plugged into Receptacle (2 cases)

For reference, Figure B-1 shows the graphic from the user manual on how to properly insert the sensor so that the tab on the sensor snaps into the slot of the sensor receptacle. Figure B-1 also shows an image of a properly inserted sensor into a receptacle on a patient.

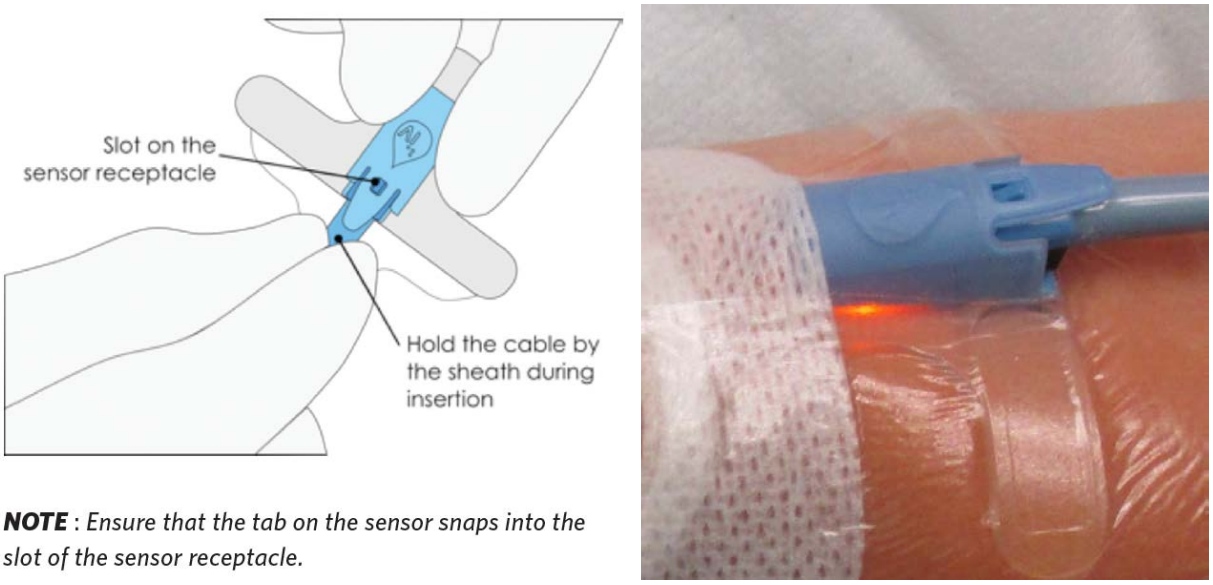

Figure B-1. graphic from the ivWatch Model 400 user manual on how to properly insert a sensor into a receptacle (left), and a zoomed-in image of a properly connected sensor and receptacle (right)

In the site images for CRF numbers 89 (Figure B-2) and 113 (Figure B-3), it was found that the sensor was not completely plugged into the receptacle at the beginning of the study. This allows the sensor to slide in and out of the receptacle when the patient moves, and can lead to unstable / unexpected optical signals. Images from these cases are shown below.

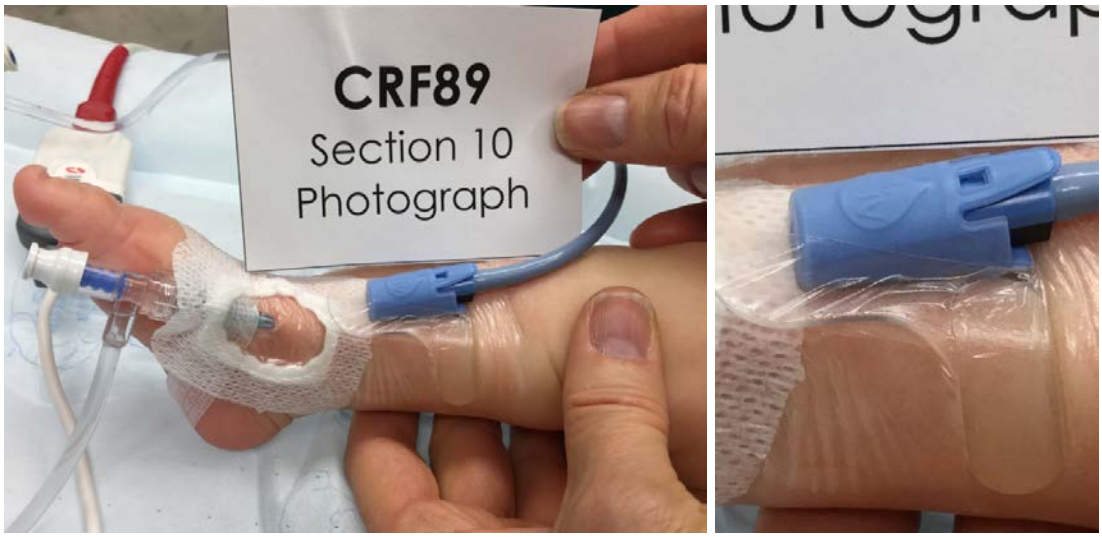

Figure B-2. CRF 89 site image (left) and zoomed-in on the sensor receptacle connection (right), showing incomplete insertion.

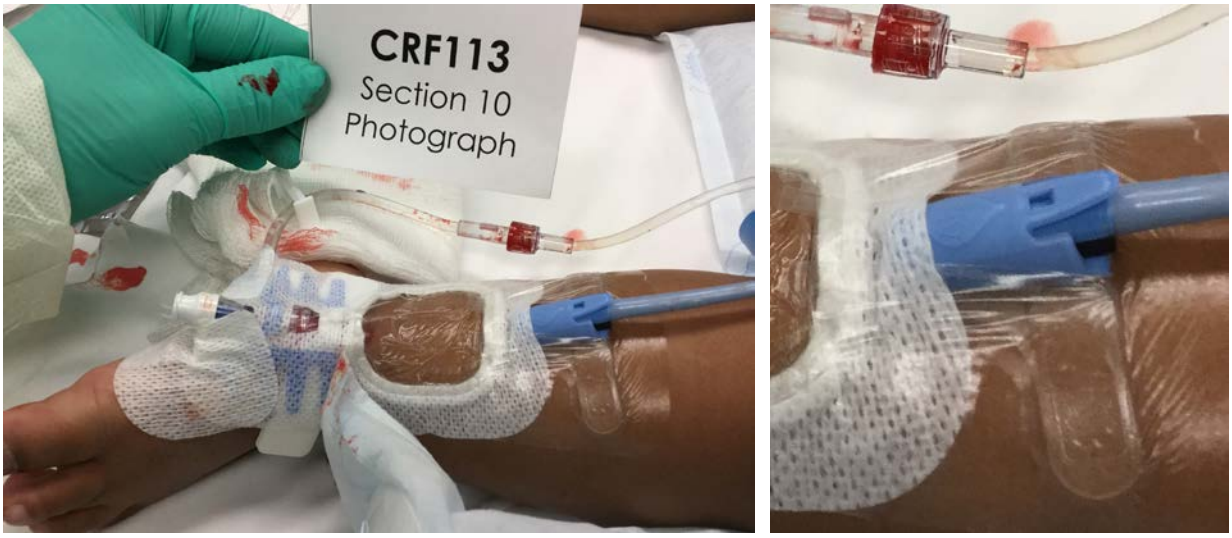

Figure B-3. CRF 113 site image (left) and zoomed-in on the sensor receptacle connection (right), showing incomplete insertion.

Receptacle Placed over White Mesh (1 case)

For CRF 124 (Figure B-4), the optical sensing portion of the sensor was placed over the white mesh portion of the occlusive dressing. The nurses were trained to not place the sensor over the white mesh, because the optical signals cannot penetrate this material.

Figure B-4. CRF 124 site image (left) and zoomed in on the receptacle location (right), showing placement over the white mesh border of occlusive dressing.

Appendix C Subject Demographics

Tables C-I and C-II show the subject demographics for the accepted cases in the non-alarming and alarming groups, respectively. There were several other data fields collected in the case report forms that are not shown in this table, including catheter gauge / length, immobilization option, IV Site analgesia, ultrasound guidance, IV fluids and medications, and post-study IV assessments.

Table C-I. Non-Alarming Group Demographics

CRF	Gender	Age	Age Units	Weight (kg)	Skin Color	Site	Infiltration
1	male	2.5	months	4.5	light	forearm	no
2	female	15	years	56.2	light	forearm	no
3	male	10	years	34.5	light	hand	no
4	female	12	years	64.6	light	forearm	no
5	male	10	years	63.5	light	forearm	no
6	female	6	months	7.0	light	leg	yes
7	female	16	years	94.3	light	forearm	no
8	female	15	months	13.3	light	foot	no
9	female	11	years	53.9	dark	forearm	yes
10	male	12	years	129.0	light	forearm	no
11	male	6	years	27.9	light	forearm	no
12	female	3	years	15.5	light	hand	no
13	male	2.5	years	10.0	medium	forearm	no
15	male	15	months	31.4	medium	forearm	no
16	female	16	years	73.0	light	hand	no
17	male	18	months	13.6	light	forearm	no
18	male	9	months	6.7	light	forearm	no
20	male	14	years	51.0	light	hand	no
21	female	12	years	47.9	light	forearm	no
22	male	12	years	39.1	medium	hand	no
23	female	4	years	18.2	dark	hand	yes
25	female	4	years	15.8	light	hand	no
26	male	5	years	16.6	medium	forearm	no
28	female	3	months	5.1	light	hand	no
29	male	0.75	months	3.3	light	foot	yes
30	female	14	years	61.0	light	forearm	no
32	female	6	years	27.7	medium	foot	no
33	female	4	years	13.0	light	foot	no
34	male	4	months	5.3	light	foot	no
35	female	15	years	53.7	light	hand	no
36	male	3	months	7.2	light	forearm	yes
37	female	12	months	6.8	dark	forearm	yes
39	female	6	years	20.1	light	hand	no
40	female	2	years	11.0	medium	hand	no
41	female	13	years	59.1	light	hand	no
43	male	7	years	24.7	light	forearm	no
44	male	4	months	6.3	dark	forearm	no
45	female	12	years	22.8	light	hand	no
46	male	1	months	4.4	light	hand	no
47	male	3	years	13.5	light	forearm	no
48	male	16	years	85.2	light	forearm	no
49	female	7	years	23.7	light	forearm	no
50	male	4	years	17.4	light	hand	no
51	female	12	years	36.7	light	hand	no
52	female	13	years	58.7	light	forearm	no
53	male	17	years	126.3	light	hand	no
54	female	7	years	23.1	light	hand	no
56	male	2	years	12.2	medium	hand	no
57	male	3	years	12.5	light	forearm	no
58	male	16	months	6.5	light	forearm	no
59	female	15	years	73.0	light	forearm	no
60	male	10	months	10.3	dark	forearm	no

CRF	Gender	Age	Age Units	Weight (kg)	Skin Color	Site	Infiltration
61	female	15	years	79.7	light	hand	no
62	male	4	years	15.7	light	forearm	no
63	female	15	years	91.9	light	forearm	no
64	male	2	years	11.1	light	forearm	no
65	female	10	years	30.3	light	forearm	no
66	female	16	months	9.7	light	hand	no
67	male	20	months	12.2	light	forearm	no
68	female	14	years	47.0	light	forearm	no
69	male	5	years	19.9	medium	forearm	no
70	male	2	years	14.5	light	forearm	no
71	female	17	years	58.6	light	hand	no
72	female	2	years	10.6	light	forearm	no
74	male	10	years	36.7	light	hand	no
75	female	9	years	43.6	light	hand	yes
76	female	17	years	75.3	light	hand	no
78	male	7	years	38.1	light	forearm	yes
79	female	10	years	18.5	light	hand	no
80	female	13	months	18.5	light	hand	no
81	female	1	years	11.9	medium	hand	no
82	female	23	months	10.3	light	forearm	no
83	male	11	years	61.2	light	forearm	no
84	female	16	years	95.4	light	forearm	yes
85	female	14	years	52.3	light	hand	no
86	male	2	years	13.0	light	leg	no
87	female	10	years	40.7	light	forearm	no
88	male	6	years	27.4	dark	hand	no
90	female	12	years	40.2	light	hand	no
91	male	3	years	17.6	medium	hand	no
92	male	2	years	14.1	light	hand	yes
93	male	9	months	5.9	light	foot	no
94	female	10	years	27.1	light	hand	no
96	female	6	years	22.7	light	hand	no
97	male	4	months	6.4	light	hand	no
98	female	2	years	16.3	light	hand	no
99	male	3	years	18.7	medium	forearm	no
100	female	16	years	50.4	light	forearm	no
101	female	11	years	26.3	light	a/c	yes
102	male	4	years	16.3	light	hand	no
103	female	5	years	17.9	light	forearm	no
104	male	3	years	15.1	medium	hand	no
106	male	14	years	47.7	light	forearm	no
107	male	14	months	8.3	light	forearm	no
108	male	7	years	23.0	dark	hand	no
110	female	1	months	3.8	light	hand	no
111	male	13	years	79.6	light	hand	yes
112	male	17	years	58.9	light	forearm	no
114	male	3	years	12.9	light	hand	yes
115	male	17	months	10.4	light	foot	no
117	male	19	months	10.7	light	hand	no
118	female	14	years	132.2	light	forearm	no
119	male	16	years	89.7	light	hand	no
120	male	7	years	28.0	dark	hand	no
121	female	7	years	28.0	light	hand	no
122	male	14	years	32.5	light	hand	no
123	female	16	years	53.7	light	forearm	no
125	female	13	years	53.1	light	forearm	no
126	male	5	years	20.6	light	hand	no
127	male	3	months	7.2	light	forearm	no
129	male	13	years	33.2	light	hand	no
130	female	6	years	23.4	light	hand	yes
131	female	11	years	36.2	light	hand	no
132	female	12	years	45.2	light	hand	no
133	female	13	years	64.6	light	hand	no
135	female	8	years	28.0	light	forearm	no

CRF	Gender	Age	Age Units	Weight (kg)	Skin Color	Site	Infiltration
137	male	2	years	14.2	dark	hand	no
138	female	12	years	44.7	light	forearm	no
141	male	15	years	51.9	light	hand	no
142	male	2	years	11.7	medium	hand	yes
144	female	11	years	31.1	dark	hand	no
146	female	13	years	51.7	medium	hand	no
147	female	9	years	17.1	light	forearm	no
148	male	10	years	33.4	light	hand	no
150	female	2	years	15.7	medium	hand	yes
152	female	2	years	12.7	light	forearm	yes
153	male	7	years	31.7	light	forearm	no
154	female	16	years	63.0	light	forearm	no
155	female	8	months	7.0	light	hand	yes
156	male	11	years	60.8	dark	hand	no
157	male	5	months	8.0	light	hand	no
158	female	8	years	42.4	light	hand	no
159	female	6	years	15.2	light	forearm	no
160	male	14	years	100.6	light	forearm	yes
161	male	7	years	16.4	dark	forearm	no
162	male	2	years	15.2	light	hand	no
163	female	2	years	13.9	light	hand	yes
164	female	7	years	32.1	dark	hand	no
165	female	17	years	60.3	light	forearm	no
166	male	9	years	35.5	dark	hand	yes
167	female	6	months	6.6	light	hand	yes
168	female	11	years	31.6	light	forearm	no
169	female	4	years	12.7	light	hand	no
170	female	7	years	20.0	light	hand	no
171	female	14	years	90.2	light	forearm	yes
172	male	11	years	22.0	light	hand	no
173	female	17	years	67.1	light	forearm	no
174	female	8	months	9.7	medium	forearm	no
175	male	17	months	7.8	light	hand	no
177	female	13	years	45.2	light	forearm	no
178	male	17	years	196.7	dark	hand	no
179	female	8	years	19.4	medium	hand	no
182	male	17	months	11.6	light	forearm	no
183	female	14	years	53.0	dark	hand	no
184	male	10	years	28.9	light	forearm	no
185	female	8	years	31.8	dark	forearm	no

Table C-II. Alarming Group Demographics

CRF	Gender	Age	Age Units	Weight (kg)	Skin Color	Site	Infiltration
186	male	14	months	9.0	light	forearm	no
187	female	16	years	54.3	light	hand	no
188	male	7	years	28.7	dark	forearm	no
189	female	8	years	26.8	dark	forearm	no
190	male	2	years	12.9	light	forearm	no
191	male	0.5	months	3.5	medium	hand	no
192	male	3	years	14.7	medium	hand	no
193	female	17	years	45.3	light	forearm	no
194	male	16	years	89.2	light	hand	no
195	female	2	years	11.3	light	forearm	no
196	male	8	years	28.1	light	forearm	no
197	male	16	months	9.9	dark	hand	yes
198	male	23	months	10.2	dark	forearm	yes
199	female	13	years	60.1	light	forearm	no
200	male	11	years	30.5	light	forearm	no
201	female	4	months	7.0	light	hand	no
202	female	16	years	64.1	light	forearm	no
203	male	12	years	81.5	dark	forearm	yes
204	male	8	months	8.4	light	forearm	no
205	female	16	years	120.7	light	forearm	yes
206	male	2	years	13.7	light	forearm	no
207	female	12	years	37.6	light	forearm	no
208	female	7	years	33.2	light	forearm	no
209	male	8	months	10.0	light	forearm	no
210	female	2	years	13.7	light	hand	yes
211	female	2	years	13.4	light	hand	no
213	female	12	years	73.0	light	hand	no
214	female	9	years	126.8	light	hand	no
215	female	9	years	20.4	light	forearm	no
216	female	8	months	7.3	light	forearm	yes
217	male	9	months	18.4	light	forearm	no
218	female	13	years	42.2	light	forearm	yes
219	male	5	years	20.8	dark	forearm	no
220	female	16	years	75.3	light	forearm	yes
221	female	23	months	12.0	light	forearm	no
222	female	9	months	7.7	light	forearm	no
223	male	11	years	57.2	dark	forearm	no
224	male	17	years	84.2	light	forearm	yes
225	male	4	years	18.3	light	hand	no
226	female	4	years	17.1	light	hand	yes
227	female	8	years	27.4	light	hand	no
228	male	2	years	16.1	dark	hand	no
229	male	6	years	15.7	light	hand	no
230	male	13	years	65.5	light	forearm	yes
231	male	17	years	83.1	light	hand	no
232	female	10	years	52.9	medium	hand	yes
233	male	7	years	27.4	light	hand	no
234	female	5	years	22.1	light	hand	no
235	male	22	months	10.1	light	hand	yes
236	female	8	years	26.1	light	hand	no
237	male	11	months	9.0	light	forearm	no
238	female	16	years	44.7	light	forearm	no
239	female	4	years	19.3	light	hand	yes
240	female	13	months	10.3	dark	hand	yes
241	female	13	years	39.6	light	forearm	no
242	female	3	years	13.2	dark	forearm	no
243	female	15	years	122.7	light	hand	no

Appendix D Notification Rate Data

The following data was used in the calculation for notification rate using a negative binomial regression model.

CRF	Number of Yellow Notifications	Number of Red Notifications	Time When Yellow Notification Possible (hrs)	Time When Red Notification Possible (hrs)	Infiltration
186	0	0	35.885	35.885	no
187	0	0	24.888	24.888	no
188	0	0	38.039	38.039	no
189	0	0	49.630	49.630	no
190	0	0	50.030	50.030	no
191	1	0	17.174	18.288	no
192	0	0	54.589	54.589	no
193	0	0	115.409	115.409	no
194	0	0	68.870	68.870	no
195	0	0	104.571	104.571	no
196	0	1	48.568	49.346	no
197	0	1	55.206	55.638	yes
198	0	1	29.389	29.395	yes
199	0	0	19.920	19.920	no
200	0	0	20.638	20.638	no
201	0	0	46.698	46.698	no
202	0	0	24.011	24.011	no
203	1	1	29.446	29.795	yes
204	0	0	70.064	70.064	no
205	0	1	14.940	14.970	yes
206	0	0	25.856	25.856	no
207	2	1	53.675	56.892	no
208	0	1	27.871	28.977	no
209	1	1	60.428	61.255	no
210	0	1	70.260	70.814	yes
211	0	0	44.309	44.309	no
213	2	0	10.044	10.073	no
214	0	1	27.449	27.453	no
215	1	0	25.561	25.568	no
216	0	2	3.640	3.684	yes
217	0	2	100.128	100.147	no
218	0	2	82.768	88.403	yes
219	1	2	6.655	6.720	no
220	0	0	3.588	3.588	yes
221	0	0	4.996	4.996	no
222	0	0	94.451	94.451	no
223	0	0	5.742	5.742	no
224	0	0	8.800	8.800	yes
225	0	0	48.410	48.410	no
226	0	2	35.015	35.029	yes
227	0	0	22.105	22.105	no
228	0	0	46.694	46.694	no
229	1	1	20.404	20.773	no
230	0	1	8.284	8.975	yes
231	0	0	53.922	53.922	no
232	0	1	32.606	32.619	yes
233	0	1	46.214	46.223	no
234	1	1	39.231	39.840	no
235	0	2	14.898	15.844	yes
236	0	0	2.612	2.612	no
237	0	2	68.867	68.903	no
238	0	0	76.188	76.188	no
239	0	0	30.509	30.509	yes
240	0	1	12.562	13.564	yes
241	0	1	17.538	18.057	no
242	4	4	51.340	53.140	no
243	0	0	37.327	37.327	no

Appendix E Adverse Events

Two adverse events were recorded in the study, for CRF numbers 100 and 120. Both were recorded as "mild non-serious events".

CRF 100

The case report form for this subject notes there was a red area on the skin, near the sensor. In the post-study site image for this subject (Figure E-1), a red area is seen at the antecubital fossa, near the ivWatch receptacle edge.

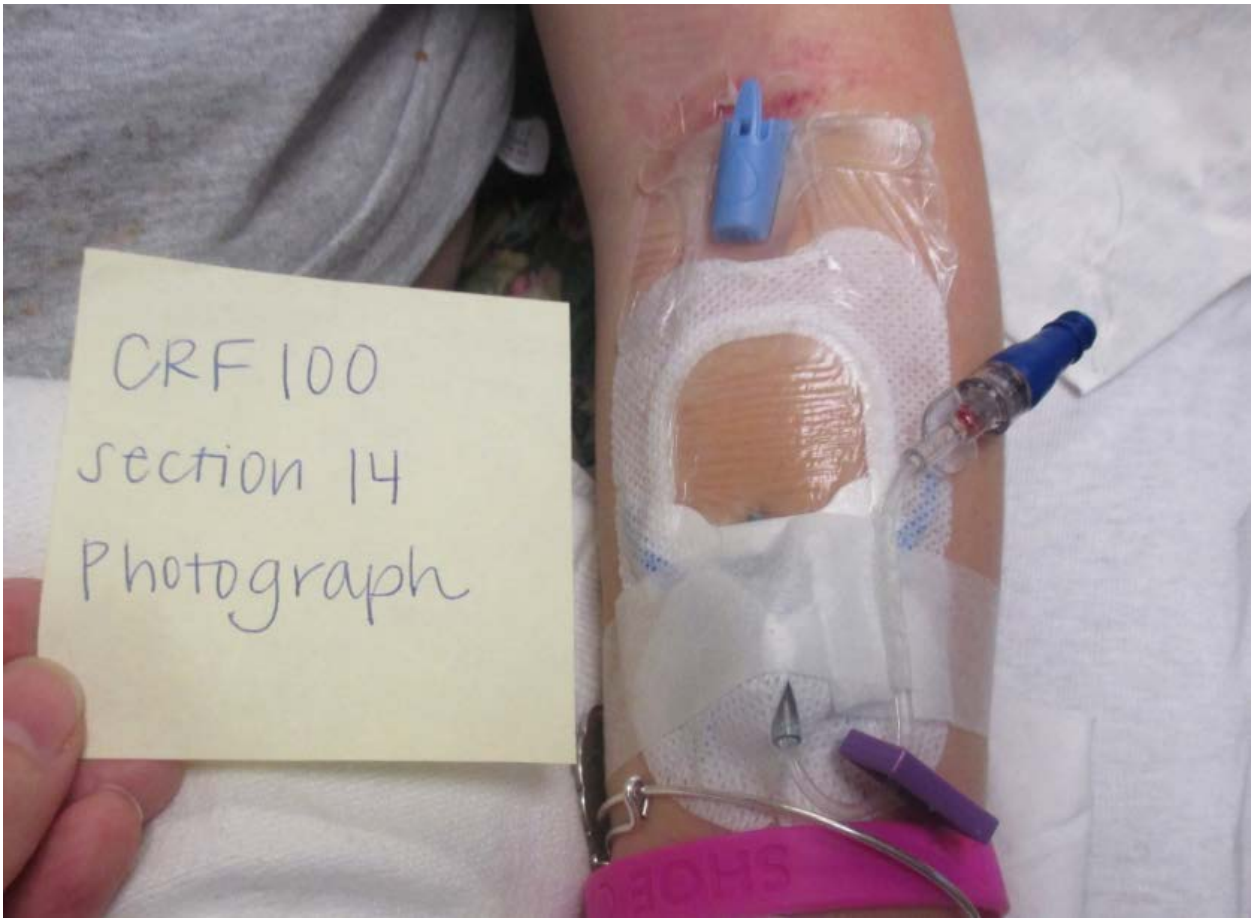

Figure E-1. Post-study image for CRF 100 showing a red area at the antecubital fossa

CRF 120

The subject complained of pain, the bedside RN noted skin blanching under the ivWatch receptacle. The RN noted that the event may be due to the "movement of skin under sensor". The post-study site image for CRF 120 is shown in Figure E-2. Skin blanching is noted in the wrist area.

Figure E-2. Post-study image for CRF 120 showing skin blanching near the wrist

Appendix F Investigator Signatures

Investigator Signatures

Study Title Optical Detection of Intravenous Infiltration: A Pilot Study – Phase II

Report Author William J. Naramore, CTO, IvWatch

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Principal Investigator

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Affiliation: Cincinnati Children's Hospital Medical Center
Signature: D Doellman RN
Date: 8/29/16

Investigator

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