A Safer Care Pathway from ICU to Home with wearable & wireless monitoring

Martine Breteler

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Een veiliger zorgpad van IC naar huis

met draagbare & draadloze monitoring

(met een samenvatting in het Nederlands)

Proefschrift

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Universiteit Utrecht
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door

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Chapter 1

General introduction

Introduction

Surgery plays an integral role in preventing death and disability and may thus improve quality of life. When patients after major surgery reach the post anaesthesia care unit, families think they have survived the most dangerous part of their perioperative pathway. This assumption is wrong. At least 4.2 million people worldwide die within 30 days of surgery each year [1]. In addition, mortality in the post-surgical period attributable to postoperative adverse events is more than 90 times higher than intraoperative mortality [2-4]. Not only surgical patients, but also other medical ill patients are at risk for adverse events. In a cohort study of 400 medical patients, nearly 20% experienced adverse events after discharge, of which nearly three-quarters could have been prevented [5,6]. The majority of adverse events are preceded by a significant period of change in vital signs [7-10]. In current routine practice, clinicians rely on 'spot checks' of vital signs to identify adverse events early. However vital signs are typically only measured once every 8-h shift. As a result, early signs of clinical deterioration may be easily overlooked. Especially at night, when a critical condition of a patient could worsen until the next morning, without being noticed [11-13].

To improve early recognition and adequate treatment for deteriorating patients, Rapid Response Teams (RRT) have been introduced worldwide [14,15]. But even in hospitals with an established RRT, failure to rescue events occur, mostly related to the 'afferent limb' of the system, e.g. failure to identify patients at risk [16]. With the current low monitoring frequency early warning signals, such as periods of hypotension or hypoxaemia, on hospital wards will be missed, even though these periods occur frequently. For example, a recent study showed that 47% of postoperative patients develop hypotensive periods with a mean arterial pressure < 65 mmHg for at least 15 minutes [17], while another study showed that more than one third of surgical patients experience an oxygen saturation level of <90% for an hour or more [18]. Increasing the intensity of patient observations by more frequent nursing rounds may seem a logical approach, but is unlikely given the limited availability of trained nurses and budget constraints.

Continuous vital signs monitoring could contribute to earlier recognition of the deteriorating patient, especially in 'low-care' environments, such as the general ward or at home. It may facilitate automated notification of clinical deterioration, initiate early therapeutic interventions and it has been associated with a reduced need for patient rescue events or ICU transfers [19,20]. Several wireless and wearable devices intended for vital signs monitoring are now available on the market and are capable of recording several vital signs, such as heart rate,

respiratory rate, temperature and motion. These sensors even allow the patient to mobilize early without being hindered by any wires from a ICU-grade monitor.

Such wireless monitoring technology combined with appropriate communication- and intervention facilities could even be used for patients to recover at home by allowing early and safe discharge. Following hospital discharge, patients are typically disconnected from medical supervision and no longer monitored at all, while hospital admissions shift to much shorter stays than ever before. Although recovery in the patient's familiar home situation has many benefits, unrecognized vital instability and mortality after hospital discharge still occurs [21]. In a cohort of 40.004 patients after noncardiac surgery, 1.8% died within 30 days after surgery, of which more than 29% of the deaths occurred at home after hospital discharge [22]. In addition, hospital readmissions in patients after major surgery occur frequently, ranging from 5%-19% and are associated with poor outcomes [21,23-25]. This suggests the need for safer discharge with remote monitoring of vital signs and symptoms to recognize the early signs of clinical deterioration in patients at risk for complications in the first days at home.

All foregoing numbers indicate that, at least in theory, health benefits could be achieved if continuous remote monitoring would become available to ensure an appropriate and timely response if patient deterioration occurs on the general ward or during the early days at home after hospital discharge. We hypothesize that wireless and wearable monitoring solutions can only contribute to improved patient outcomes if these sensors are critically validated in a clinical setting and able to detect adverse events. Moreover, we expect that remotely observing vital signs in patients discharged home is technically feasible and accepted by patients and care professionals. In addition, the requirements needed for successful development and implementation of a wireless patient monitoring solution from hospital to home is largely unknown and further explored. Regarding the overarching aim, we hypothesize that empowering care professionals and patients with wireless and wearable technology for vital signs monitoring that uses optimized detection algorithms for impending deterioration will enhance patient safety within hospital and at home, improve patient outcomes and quality of life for patients and their relatives and reduce healthcare costs.

Outline of this thesis

This thesis is divided into three parts. Part 1 focuses on the validation of different wireless and wearables sensors for continuous vital signs monitoring to detect patient deterioration in a clinical setting (chapter 2, 3 and 5) and the evaluation

of these systems to detect adverse events in patients outside high-care facilities (chapter 4). In Chapter 2, a critical validation of a wireless patch sensor for continuous vital signs monitoring is performed in high-risk surgical patients at a step-down unit. Chapter 3 elaborates on Chapter 2 and includes the validation of the measurement performance of multiple commercially available wireless monitoring systems. In chapter 4, the capability of wireless monitoring systems to detect adverse events in patients at the step-down unit and general ward is evaluated. Finally, chapter 5 describes a proposed test protocol to assess the reliability and usability of new (prototype) wireless wearable sensors for continuous vital signs monitoring. Part 2 discusses the potential of home monitoring of patients at risk for deterioration after hospital discharge. Chapter 6 describes the feasibility of home blood pressure monitoring in patients following carotid endarterectomy after hospital discharge. In chapter 7, remote monitoring of vital signs trend patterns in patients discharged early after esophagectomy is evaluated. Part 3 provides an organizational perspective on remote patient monitoring from hospital to home. A methodological approach to include stakeholder perceptions in the design of wireless patient monitoring solutions is conducted in chapter 8. In chapter 9, a general discussion with lessons learned and future directions for remote patient monitoring from hospital to home is provided.

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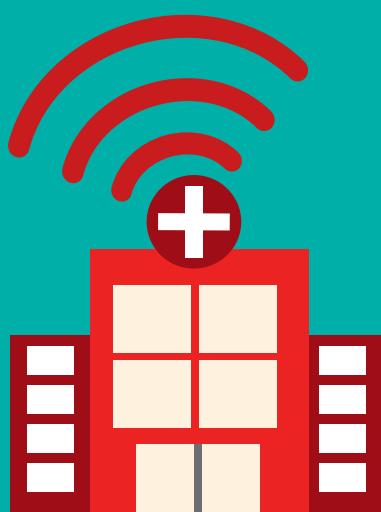
PART 1

Measurement performance of wearable wireless vital signs sensors to detect patient deterioration
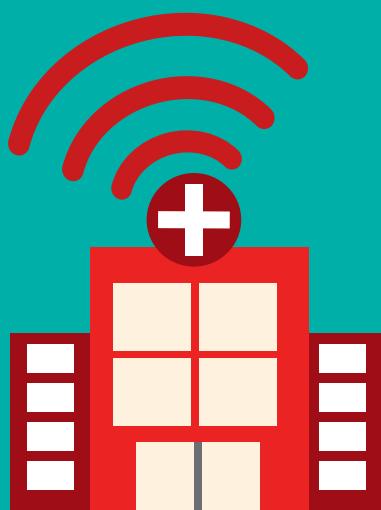
Chapter 2

Reliability of wireless monitoring using a wearable patch sensor in high-risk surgical patients at a step-down unit in the Netherlands: a clinical validation study

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Abstract

Background and objectives: Intermittent vital signs measurements are the current standard on hospital wards, typically recorded once every 8h. Early signs of deterioration may therefore be missed. Recent innovations have resulted in 'wearable' sensors, which may capture patient deterioration at an earlier stage. The objective of this study was to determine whether a wireless 'patch' sensor is able to reliably measure respiratory and heart rate continuously in high-risk surgical patients. The secondary objective was to explore the potential of the wireless sensor to serve as a safety monitor.

Design: In an observational methods comparisons study, patients were measured with both the wireless sensor and bedside routine standard for at least 24 hours.

Setting: University teaching hospital, single center.

Participants: Twenty-five postoperative surgical patients admitted to a step-down unit.

Outcome measures: Primary outcome were limits of agreement and bias of heart rate and respiratory rate. Secondary outcome measures were sensor reliability, defined as time until first occurrence of data loss.

Results: 1568 hours of vital signs data were analyzed. Bias and 95% limits of agreement for heart rate were -1.1 (-8.8 to 6.5) beats per minute. For respiration rate, bias was -2.3 breaths per minute with wide limits of agreement (-15.8 to 11.2 breaths per minute). Median filtering over a 15 minute period improved limits of agreement of both respiration and heart rate. Sixty-three% of the measurements were performed without data loss greater than two minutes. Overall data loss was limited (6% of time).

Conclusions: The wireless sensor is capable of accurately measuring heart rate, but accuracy for respiratory rate was outside acceptable limits. Remote monitoring has the potential to contribute to early recognition of physiological decline in high-risk patients. Future studies should focus on the ability to detect patient deterioration on low care environments and at home after discharge.

Introduction

While technological advances have resulted in numerous new diagnostic tools and therapeutic innovations, we are still not able to timely recognize patient deterioration on general hospital wards[1,2]. This contributes to avoidable cardiopulmonary arrest, unplanned admission to the intensive care unit (ICU), an increase in hospitalization costs and detrimental effects on quality of life[3-7]. To timely detect patient deterioration, we may benefit from technical solutions that can track patients' vital signs continuously.

Intermittent vital signs measurements, typically once every nurse shift of eight hours, are the current routine monitoring practice on general hospital wards. As a result, patient deterioration in between measurements can be easily missed. In an attempt to improve the detection of patient deterioration, Early Warning Scoring (EWS) protocols and Medical Emergency Teams (METs) have been implemented in most hospitals around the globe. However, failure-to-rescue events continue to occur even with these systems in place[8,9]. This phenomenon is also known as failure of the 'afferent limb' of the EWS system[10-12]. Alongside the attempts to improve detection of patient deterioration on the ward, there is a trend to reduce the duration of hospitalization by discharging patients home early, for example in 'enhanced recovery after surgery' (ERAS) programs[13-15]. Once a patient is back home, EWS protocols and vital signs monitoring are no longer available. Recovery within the patient's own home environment has many advantages, but unavoidably some surgical complications will now become first manifest in the home setting. This increases the risk that patient deterioration will be recognized too late.

The majority of adverse events are preceded by a significant period of change in vital signs[16-20]. Early recognition of the deteriorating patient might be improved if continuous remote monitoring would become available for at-risk patients in 'low care' environments such as the regular hospital ward or in the first few 'critical' days at home after hospital discharge[21,22]. Recent technological innovations have resulted in lightweight 'wearable' wireless sensors capable of recording and transmitting several vital signs such as heart rate (HR), respiration rate (RR), temperature and patient movement. While the majority of the wearable sensors is strictly 'consumer-grade', some manufacturers have obtained CE and/or FDA approval for use in clinical environments. However, validity and accuracy of these so called 'medical-grade' wearables has not been

extensive assessed in real clinical environments. Two studies reported satisfactory agreement between heart rate, respiration rate of a wearable patch sensor and their respective reference devices. However, these measurements were obtained from healthy participants in controlled conditions. Another study showed reliable heart rates and respiration rates with a wearable patch sensor in the majority of patients, but these data was limited to short periods of measurements in patients with comorbid conditions[23-25]. As such, we cannot translate these findings accordingly to patients in a clinical environment at risk for complications.

The objective of this study was to determine whether a wireless adhesive 'patch' sensor is able to reliably measure RR and HR continuously in patients after high-risk surgery. We aimed to verify whether wireless sensor technology is robust and capable of detecting physiological trend patterns in high-risk patients before introducing wireless vital signs monitoring into clinical practice. A secondary objective was to explore the potential of the wireless sensor to serve as a safety monitor in clinical practice.

Materials & Methods

Study design and setting

We performed a methods comparisons study with an observational design in which patients were continuously monitored after high-risk surgery during the initial days of recovery at the surgical step-down unit (SDU) of the University Medical Center Utrecht, the Netherlands, a large academic hospital. Formal approval for this study was obtained from the local ethical committee (number 15/550).

Study participants

Postoperative patients were asked to participate upon admission to the SDU if their expected stay was at least 24 hours. These patients were considered for enrolment because they represent a high-risk subset of surgical patients that is more prone to experience deterioration compared to patients on the general ward. Exclusion criteria were patients with an implantable cardiac device, an allergy to adhesives, wound or skin lesion near the application site, or inability to give informed consent. After written informed consent was obtained, researchers applied the sensor to the patient's chest to start recording vital signs for one to three days using the wearable sensor and the routine monitoring system described hereafter.

Description of the wireless wearable sensor

The HealthPatch® MD (VitalConnect Inc, San Jose, CA, USA) is a medical-grade lightweight, wireless and wearable adhesive biosensor that measures a number of vital signs continuously: single-lead electrocardiogram (ECG), HR, heart rate variability, RR, skin temperature, body posture and step count. It was designed to facilitate long-term remote monitoring of vital signs and activity metrics within the hospital environment as well as in the post-discharge period at home. The sensor consists of a disposable adhesive patch that houses two ECG electrodes, a thermistor and a zinc-air coin-cell battery. The reusable sensor module contains a triaxial accelerometer and Bluetooth Low Energy (BLE) transceiver (see Appendix 1). The patch can be applied on the patient's chest and measures vital signs continuously up to three days (four days if continuous transmission of its single lead ECG waveform is disabled). The module processes the incoming signals and transmits the data via BLE to a relay device (for this study we used an iPad mini (Apple, Inc. Cupertino, CA, USA) with the 'Healthwatch' (VitalConnect Inc, San Jose, CA, USA) mobile application. This application can display vital signs data in real-time for research purposes, but was not designed to be used as clinical monitoring system. Also, near real-time data can be viewed on the Healthwatch Web cloud based server, to monitor long-term trends. Quality of the sensor data was verified several times by the researchers during data collection. Patient identification information was not entered on the mobile device to ensure privacy protection.

Although the wireless sensor can also measure position, in this study we only focused on assessing the accuracy and reliability of RR and HR monitoring. The sensor calculates HR using analysis of the single-lead ECG. The algorithm is based on automated detection of QRS complexes from the ECG waveforms. RR is derived from the combined information from three sources: an embedded algorithm uses a weighted average of two characteristics of the ECG signal: 1.) QRS amplitude modulation and 2.) respiratory sinus arrhythmia (RSA); both ECG-derived signals change during inspiration and expiration[26], and the algorithm uses 3.) accelerometer data produced by chest movement during respiration [27]. Both HR and RR are updated every 4 s and the manufacturer states an accuracy of ± 3 breaths per minute (breaths/min), in the range of 4 to 42 breaths for RR. The stated accuracy of HR is ± 5 beats per minute (beats/min) or 10% (whichever is greater), in the range of 30-200 beats/min.

Description of the bedside routine standard

HR and RR of patients were continuously monitored with the wearable sensor and simultaneously with a multiparameter bedside monitoring system designed

for use in ICU's and Operating Rooms (XPREZZON, Spacelabs Healthcare, Snoqualmie, Washington DC, USA) which served as the reference monitor. This reference uses ECG for HR detection and measures RR by thoracic impedance pneumography.

Signal analysis

The raw data transmitted by the sensor containing the measurements and their associated time stamps were retrieved in CSV format. Data were stored and processed using Matlab (The MathWorks Inc., Natick, MA, USA). Empty or invalid data ('not-a-number') were removed to obtain continuous 2D vectors of vital sign samples with their corresponding time stamps. Data reports were automatically retrieved from the reference monitor. These contained vital signs data sampled once per minute (i.e., one measurement was saved and transmitted every minute). The sensor data, originally transmitted once every four seconds was therefore resampled to once per minute (i.e., one sample per minute of the sensor was retained corresponding to the neareset time point of the reference monitor) to produce paired data points with the reference monitor. Furthermore, sensor data and reference data were synchronized to ensure alignment of their respective time stamps. No artifact removal was applied to the data before analysis.

Besides the analysis on vital signs data transmitted every minute, a median filter over a 15-minute period was applied to study the effect on HR and RR outliers and to further explore the potential of the wireless sensor in clinical practice. This filtering was calculated as a median over subsequent epochs of 15 minutes.

Outcomes

The primary outcome was bias and precision (95% Limits of Agreement; LoA) of HR and RR of the wireless sensor compared to the bedside monitor. This reference standard reports an accuracy for HR of ±1% or 3 beats/min (whichever is greater) and an accuracy of ±5% or 1 breaths/min (whichever is greater) for RR[28]. We considered HR and RR to be acceptable for clinical purposes if within ± 10% of the reference monitor or ± 3 breaths/min or ± 5 beats/min[29]. A secondary endpoint was the reliability of detecting true critical clinical conditions such as bradycardia (HR < 50 beats/min), tachycardia (HR > 100 beats/min), bradypnea (RR < 12 breaths/min) and tachypnea (RR > 20 breaths/min)[30]. Another secondary outcome was the reliability defined as time until the first occurrence of data loss (defined as a duration of a gap within the data of 2 minutes, 15 minutes, 1 hour or 4 hours) and the overall amount of data loss from various causes.

Statistical analysis

The series of observation pairs of HR and RR measurements (one data point every minute) derived from the wireless sensor and the reference monitor were compared using the Bland and Altman Method for repeated measurements[31]. This method was used to account for within-subject variation by correcting for the variance of differences between the average differences across patients and the number of measurements per patient. The mean difference ('bias') between the wireless sensor and reference monitor and the 95% LoA (± 1.96 SD) was determined for both the HR and RR data. In addition, a Clarke Error Grid analysis was conducted to specify the clinical accuracy and the consequences for clinical decision making[32]. The time (hours) to first occurrence of data loss was analysed with Kaplan-Meier survival plots.

A power calculation was not feasible due to the lack of preliminary data with these continuous monitoring systems. Therefore, we aimed to analyze data of at least 25 patients - each with multiple hours of continuous data – which is sufficient to evaluate the validity of the wireless patch sensor.

Results

From September 2015 to September 2016, a total of 33 postoperative patients entered the study. Data from the reference monitor were missing for eight patients due to technical issues with retrieving the data from the monitor's on-board memory, resulting in a total of 1568 hours of monitoring time with the reference monitor and 1702 hours of vital signs monitoring from the wireless sensor. Therefore, measurement pairs of 25 patients were available for agreement analysis. On average, 62 hours remained per patient for further analysis. The range of total monitoring time per patient varied from 12 to 124 hours. Table 1 summarizes patient characteristics and surgical procedures .

Example of a patient measurement

Figure 1 shows the HR and RR trend during the first four postoperative days of a 60-year-old male patient with extensive cardiac and vascular comorbidities, after an open nephrectomy procedure for a suspected carcinoma in situ. Three events can be recognized: 1.) a sudden HR increase on Thursday evening; later diagnosed as atrial fibrillation, 2.) an episode of bradycardia on Saturday afternoon, and 3.) mild tachycardia and a subtle increase in RR starting Sunday afternoon, caused by bleeding from an aortic branch artery. After coil embolization, the patient was

readmitted to the Intensive Care Unit (ICU). This example illustrates agreement between HR and RR measurements recorded with the wireless sensor and the reference standard. Note that RR derived from the reference monitor was highly variable compared with RR from the wireless sensor (Figure 1).

Table 1. Patient characteristics (n = 25)

Characteristic	Value
Male gender - number (%)	18 (72)
Age (years) - median (IQR) [range]	63.0 (57.8-71.5) [23.0 – 77.0]
Body Mass Index (BMI; kg/m^2)* - median (IQR) [range]	26.2 (24.2-29.4) [17.2 - 40.2]
ASA score	
1-2 (%)	8 (32)
3-4 (%)	17 (68)
Comorbidities	
Hypertension - no (%)	8 (32)
Cardiovascular disease - no (%)	9 (36)
COPD - no (%)	3 (12)
Diabetes - no (%)	3 (12)

IQR: interquartile range. COPD: Chronic Obstructive Pulmonary Disease. * BMI of one patient was missing
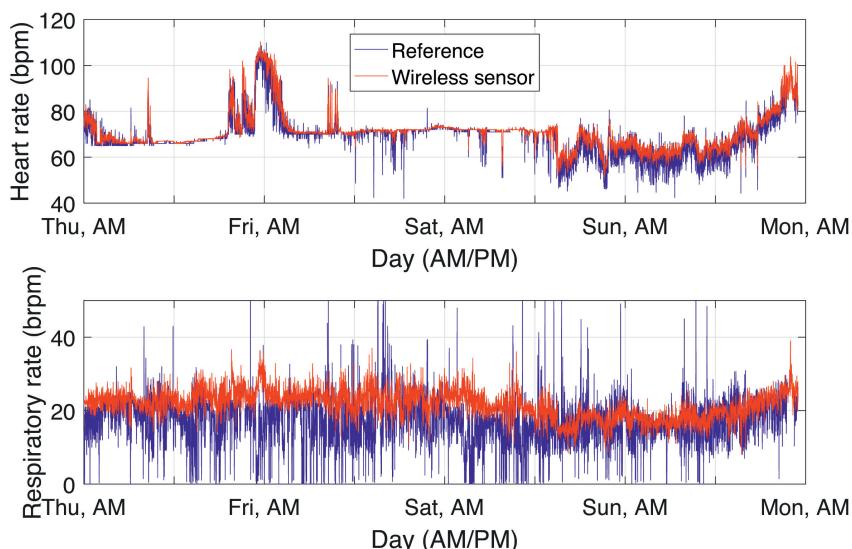

Figure 1. Example of a patient that is being measured for four days continuously with the wireless sensor (red) and reference standard (blue). The upper panel shows heart rate in beats per minute, the lower shows respiratory rate in breaths per minute.

Heart rate

Table 2 shows bias and precison (95% LoA) from comparisons between the wireless sensor and the reference standard. For analysis, 55565 minutes (926 h) of HR measurement pairs were available. The mean difference (bias) in HR was -1.1 beats/min (reference standard minus sensor) with a 95% LoA of -8.8 to 6.5 beats/min. Applying a 15 min median filter resulted in a narrower 95% LoA of -5.7 beats/min to 3.2 beats/min (3986 minutes available for analysis). Bland and Altman plots for the complete and filtered HR datasets are shown in Figure 2a and 2b, respectively.

Respiratory rate

The mean difference between the reference monitor and the wireless sensor was -2.3 breaths/min with wide levels of agreement (95% LoA: -15.8 to 11.2 breaths/min). The agreement between both methods improved after applying a 15 minute median filter, resulting in a 95% LoA of -10.8 to 5.9 breaths/min. Bland and Altman plots for the complete and filtered RR dataset are displayed in Figures 3a and 3b. Most 'high RR' outliers originated from the reference monitor and were observed in the higher RR range. This is also shown in Figure 1 where RR measurements derived from the reference monitor showed a higher variation compared with RR derived from the wireless sensor. This high variation reduced after applying a median filter over 15-minutes.

Table 2 Bland Altman analysis of wireless heart rate and respiratory rate versus reference monitor in postoperative patients

Parameter	Number of measurement pairs	Bias	SD	Lower 95% LoA[b]	Upper 95% LoA[b]
Complete dataset					
Heart rate	55565	-1,1	3,83	-8,8	6,5
Respiratory rate	56674	-2,3	6,8	-15,8	11,2
Filtered dataset[a]					
Heart rate	3986	-1,2	2,2	-5,7	3,2
Respiratory rate	4001	-2,4	4,2	-10,8	5,9

[a] *Dataset after applying a median filter*
[b] *LoA limits of agreement*
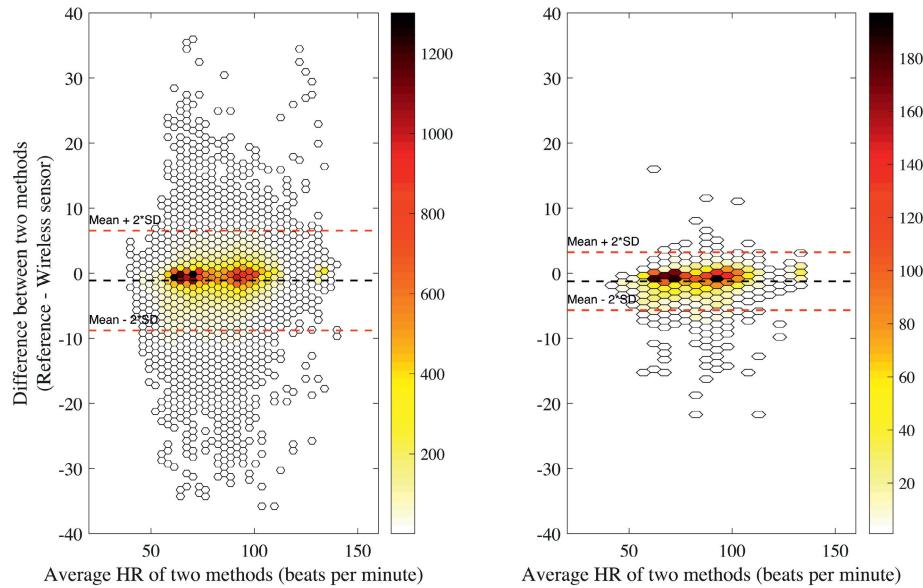
Figure 2. Bland and Altman plots for complete (left panel) and filtered (right panel) datasets for heart rate during admission at the surgical step-down unit with few (white) to many (dark red) measurement pairs
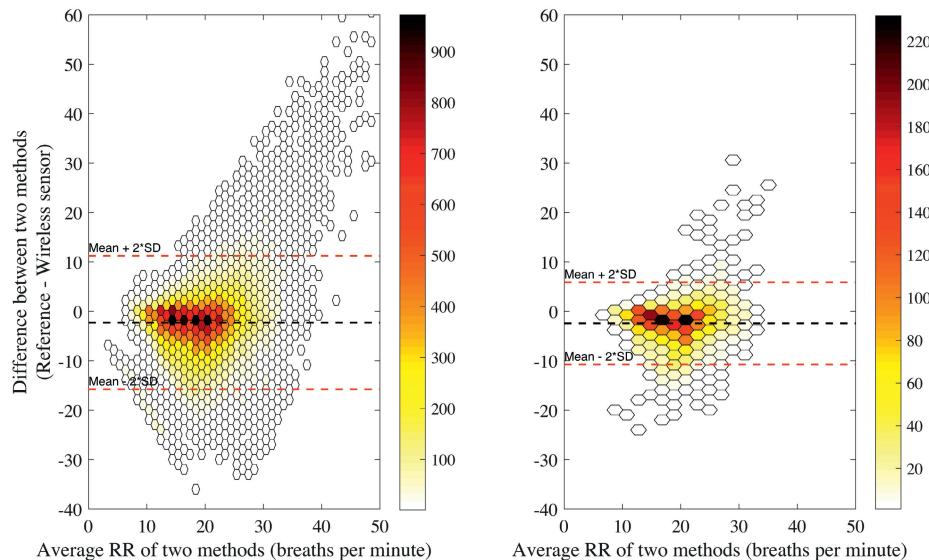
Figure 3. Bland and Altman plots for complete (left panel) and filtered (right panel) datasets for respiratory rate during admission at the surgical step-down unit with few (white) to many (dark red) measurement pairs.

Table 3. Diagnostic accuracy for bradypnea, tachypnea, bradycardia, tachycardia

	True positives (%)	False positives (%)	True negatives (%)	False negatives (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Bradycardia								
Complete dataset	824 (71)	363 (1)	55148 (99)	339 (1)	71	99	69	99
Filtered dataset[a]	24 (72)	0 (0)	3953 (100)	9 (0)	73	100	100	100
Tachycardia								
Complete dataset	7111 (90)	1490 (3)	47321 (97)	752 (2)	90	97	83	98
Filtered dataset[a]	496 (98)	65 (2)	3413 (98)	12 (0)	98	98	88	100
Bradypnea								
Complete dataset	2113 (24)	562 (1)	47438 (99)	6561 (12)	24	99	79	88
Filtered dataset[a]	134 (33)	8 (0)	3587 (100)	272 (7)	33	100	94	93
Tachypnea								
Complete dataset	16210 (84)	14602 (39)	22694 (61)	3168 (12)	84	61	53	88
Filtered dataset[a]	1225 (94)	1029 (38)	1668 (62)	79 (5)	94	62	54	95

[a] *Dataset after applying a median filter*

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Diagnostic accuracy of the wireless sensor

Because of the relatively long monitoring time per patient and the high-risk population, we were able to capture several instances of bradycardia, tachycardia, bradypnea and tachypnea. The incidence of bradycardia was rare, a HR below 50 was present in only 2% of all HR measurements in the complete dataset. Tachycardia, bradypnea and tachypnea occurred more frequently in 14%, 15% and 34% of cases respectively. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are shown in Table 3. After applying median filtering, sensitivity and specificity of all episodes with abnormal HR and RR improved.

The Clarke error grid analyses of the filtered datasets are shown in Figure 4a and 4b; it shows that 100% of the HR measurements and 99% of RR measurements are within region A or B, respectively within 20% of the reference measurement, or outside 20% of the reference but not leading to unneccesary treatment. None of the HR measurements were in region, B, C or E, which means that none of the measurements would lead to failure to treat, unnecessary treatment or confusion between bradycardia and tachycardia. Very few of the RR measurements (≤ 1 %) were within region C, D or E, indicating a potentially dangerous failure to apply the right treatment.

Technical performance

HR and RR data were recorded for the majority of the time (94%), from 36 sensors in 33 patients (Table 4). Nineteen (53%) wireless patient monitoring series had complete uninterrupted data, but in 17 patients there was data loss (ranging from 8s data loss to 60h). Most found sensor failure to be caused by a sawtooth pattern of the battery level from inadvertent covering of the air opening for the zinc-air battery resulting in measurement gaps.

Figure 5 shows the survival analysis for 'time to first failure' in data transmission of the sensor. Using a threshold (maximum duration of a gap in the data) of two minutes, this analysis showed that 63% of the wireless sensor measurements in patients were performed without data loss greater than two minutes. A gap duration of one hour resulted in 79% of sensor measurements without data loss greater than an hour.

Table 4. Amount of data loss within all wireless sensor measurements

	Time loss (hours:minutes:seconds)			
	Total loss (%)[a]	Mean loss	Minimum loss	Maximum loss
All wireless sensor measurements (n=36)	101:15:24 (5.9%)	02:48:45	00:00:00	59:59:08
Only wireless sensor measurements with any data loss (n=17)	101:15:24 (15.5%)	05:57:22	00:00:08	59:59:08

[a] *Data loss is defined as time without data as percentage of the total time measured*
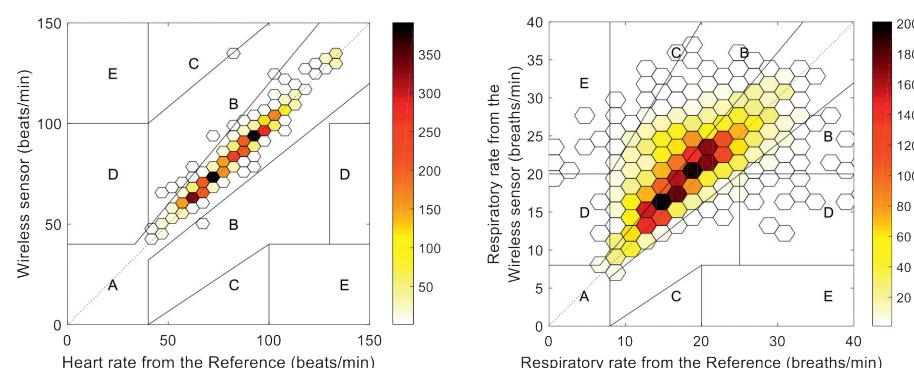
Figure 4. Clark error grid analysis to quantify clinical accuracy of the heart rate (left panel) and respiratory rate (right panel) measurements with the HealthPatch MD as compared to the reference monitor of the filtered dataset. Region (A) are points within 20% of the reference monitor, region (B) contains points outside 20% of the reference, but not leading to unnecessary treatment, region (C) are points leading to unnecessary treatment, region (D) indicates a potentially dangerous failure to detect bradycardia or tachycardia (a) or bradypnea or tachypnea (b), region (E) represents points where events are confused (e.g., bradycardia with bradypnea).
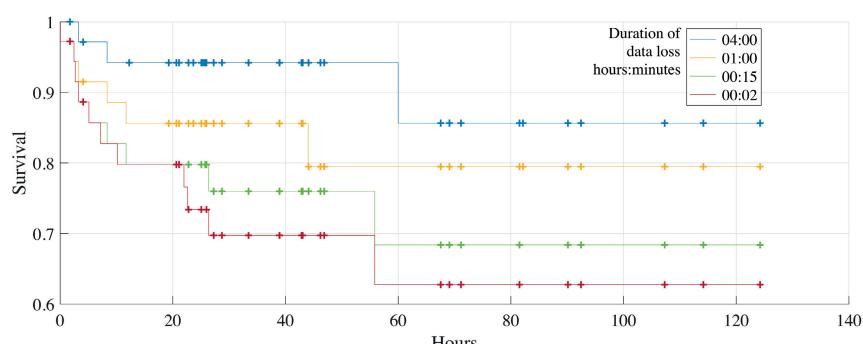
Figure 5. Survival analysis of 36 wireless sensor measurements in 33 patients versus time with various threshold times (maximum duration of a gap in the data). Data loss longer than the threshold counts as failure. The vertical marks indicate the end of a measurement other than failure (i.e., when the patient is being discharged to the ward and data transmission stopped).

Discussion

We studied the performance of a wearable wireless sensor to measure HR and RR continuously in high-risk postoperative patients. The results show that this sensor (Healthpatch MD) can accurately measure HR with a deviation within 10% of the reference standard. In contrast, the accuracy for RR was outside the limit range we considered acceptable. However, this finding may be due to frequent outliers and clinically implausible variability of RR values provided by the reference monitor. Median filtering of both signals over a 15 min period resulted in a reduction of the number of RR measurement pairs outside the acceptable LoA and an improvement of LoA. Overall, data loss was limited with HR and RR measurements 94% of the time available.

Strengths

To the best of our knowledge, this is the first clinical study that investigated the reliability and accuracy of continuous vital signs monitoring using a wearable wireless patch sensor for several days in postoperative surgical patients at a step-down unit. Most studies were actually obtained under controlled laboratory conditions[25,27,33]. These studies demonstrated the ability of the HealthPatch sensor to accurately measure HR and RR in adult participants. Hernandez et al. [24] reported a higher accuracy for HR and RR measurements with the SensiumVitals digital patch in stable patients with comorbid conditions for a limited time period (2h) compared to our study. Other studies used intermittent nurse observations on the ward as the only reference. Weenk et al. [34] reported that both HR and RR of the HealthPatch were in agreement with nurse measurements, although wide limits of agreement were found. Another study compared RR measurements of nurses with readings from the SensiumVitals digital patch and found inadequate agreement [35]. Although these studies showed the feasibility of wireless technology in clinical practice, comparison with nurse readings cannot validate the continuous performance of the wireless devices. Moreover, these wireless monitoring devices are not intended to deliver 'spot' readings for EWS, i.e., their use was evaluated for a purpose outside the intended scope of use. Consequently, a drawback of these study designs was the inability to validate continuous HR and RR measurements of new remote monitoring devices in between nurse observations. In the current study reference HR and RR were measured continuously in a clinical setting.

Limitations

The results of the present study confirm the difficulty of accurate continuous RR monitoring. However, we should also consider the limitations of the reference standard[36,37]; accuracy of thoracic impedance RR measurements can be influenced by many factors independent of breathing, such as patient movement, talking and coughing. Impedance artefacts could explain the high number of false negatives (i.e., missed bradypnea), resulting in low sensitivity. Impedance technique which is the current bedside routine standard for continuous measurement of HR and RR in most hospitals today and therefore clinically relevant. However, it cannot be considered a gold standard for RR measurement. While capnography is widely regarded as a 'true' gold standard for RR, it has several drawbacks for continuous unsupervised respiratory monitoring in spontaneously breathing patients, since its nasal cannula can be easily dislodged, leading to incomplete data and a high number of false positive 'apnea' alarms[38]. Furthermore, the HealthPatch sensor was not designed to indicate respiration rates < 5 breaths/min. Nonetheless, a progressive slowing of breathing rate may still be identified and used as indicator of vital instability, for example to recognize life-threatening opioid-induced respiratory depression.

Filtering

Applying a median filter over 15 minute data epochs improved reliability of HR and RR by removing outliers, for example, a transient very high RR caused by a movement artefact. This is appropriate since these transient artefacts (i.e., RR >45 breaths/min) are extremely unlikely from a physiological perspective. Although filtering effectively eliminates such artifacts, this comes at the expense of reducing the number of available measurements and the reduced ability to detect sudden changes in vital signs (e.g., cardiac arrest). An alternative might be to use a 'moving' median filter to keep the update rate at once every minute or once every 2 min. On the other hand, improved eliminaton of outliers could result in a higher proportion of epochs with reliable HR and RR resulting in lower false positive alarms. The latter is extremely important if this remote monitoring system is to be clinically deployed on the ward or at home. Furthermore, continuous remote monitoring on the ward with a reduced frequency (i.e., once every 15 minutes) still provides much more information regarding the patient's vital signs than the current intermittent monitoring practice, where vital signs are usually only observed once every 8h nurse shift.

In case an alarm is generated by the remote monitoring system, a nurse can personally check on the patient and correct if the cause of the alarm was not

related to a change in the patient's medical condition. However, it must be realized that a large number of false alarms is very disruptive on the general ward, especially when there is a low nurse to patient ratio (e.g., at night). This may even decrease patient safety by taking away valuable nursing time from patients who are in real need of attention. We suggest that eliminating outliers to improve reliability and eliminate false positive alerts far outweighs the limited benefits of having 'continuous' vital signs data streams.

'Methods comparison' methodology and continuous monitoring

The goal of this study was to determine whether the wireless sensor is able to reliably measure RR and HR over time in postoperative patients. Although Bland and Altman analyses can reliably indicate bias and precision of 'spot measurements', it does not inform about the 'trending ability' of the monitoring system over time, while this is of ultimate importance to timely recognize abnormal vital sign patterns. This was also confirmed in the study of Churpek et al. that showed the added value of using trends of vital signs for detecting clinical deterioration on the wards[21]. In our study, the example case in Figure 1 clearly demonstrates the ability of the wireless sensor to detect important physiological changes of a deteriorating patient over time, even while the limits of agreement for detecting bradypnea as determined by Bland Altman analyses were deemed not acceptable. Therefore, we wish to emphasize that accurate trend measurements (e.g., the ability to detect deterioration over time) is more important than just one accurate single measurement at one specific point in time.

Continuous monitoring on the general ward is still unknown territory. Future studies should therefore focus on the performance of wireless monitoring in patients at the general ward, including validation during periods of mobilization. Particular emphasis should be on the early detection of critical adverse events. However, the usability and patient perspective on remote monitoring are important to determine when creating the infrastructure of a complete remote monitoring solution.

Conclusion

Wireless continuous monitoring may have the potential to contribute to early recognition of physiological decline in high-risk patients. The tested wireless sensor was able to accurately record heart rate, but the accuracy of respiratory rate needs further optimization to reduce the incidence of false alarms and allow timely recognition of altered breathing patterns.

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Supplementary Appendix 1

Appendix 1. The HealthPatch MD consists of an adhesive patch (with 1-lead ECG and a Zinc-air battery) and a sensor module. BLE: Bluetooth Low Energy; bpm: beats per minute; brpm: breaths per minute
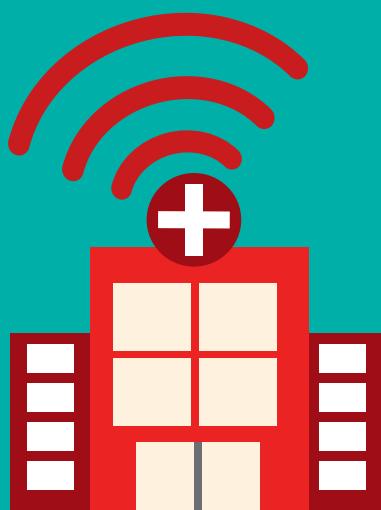
Chapter 3

Vital signs monitoring with wearable sensors in high-risk surgical patients: a clinical validation study

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Abstract

Background: Vital signs are usually recorded once every 8h in patients at the hospital ward. Early signs of deterioration may therefore be missed. Wireless sensors have been developed that may capture patient deterioration earlier. The objective of this study was to determine whether two wearable patch sensors (SensiumVitals and HealthPatch), a bed-based system (EarlySense) and a patient-worn monitor (Masimo Radius-7) can reliably measure heart rate (HR) and respiratory rate (RR) continuously in patients recovering from major surgery.

Methods: In an observational method comparison study, HR and RR of high-risk surgical patients admitted to a step-down unit were simultaneously recorded with the devices under test and compared with an ICU-grade monitoring system (Spacelabs-XPREZZON) until transition to the ward. Outcome measures were 95% limits of agreement and bias. Clarke Error Grid analysis was performed to assess the ability to assist with correct treatment decisions. In addition, data loss and duration of data gaps was analyzed.

Results: Twentyfive high-risk surgical patients were included. Over 700h of data was available for analysis. For heart rate, bias and limits of agreement were 1.0 (-6.3, 8.4), 1.3 (-0.5, 3.3), -1.4 (-5.1, 2.3) and -0.4 (-4.0, 3.1) for SensiumVitals, HealthPatch, EarlySense and Masimo respectively. For respiratory rate these values were -0.8 (-7.4, 5.6), 0.4 (-3.9, 4.7) and 0.2 (-4.7, 4.4) respectively. HealthPatch overestimated RR, with a bias of 4.4 (limits: -4.4 to 13.3) breaths/minute. Data loss from wireless transmission varied from 13% (83/633 h) - 34% (122/360 h) for RR and 6% (47/727 h) - 27% (182/664 h) for HR.

Conclusions: All sensors were highly accurate for HR. For RR, the EarlySense, SensiumVitals sensor and Masimo Radius-7 were reasonably accurate for RR. The accuracy for RR of the HealthPatch sensor was outside acceptable limits. Trend monitoring with wearable sensors could be valuable to timely detect patient deterioration.

Introduction

Changes in vital signs are an important indicator of physiological decline and hence provide opportunities for early recognition and intervention [1-4]. However, in current hospital practice nurses and physicians rely on intermittent vital signs 'spot checks' , typically once every 8 h shift. As a result, early signs of deterioration may be missed, especially at night when deterioration may progress unnoticed until the next morning [5,6]. Furthermore, compliance from nurses to vital signs monitoring protocols is often poor, in particular measurements of respiration rate [7,8], resulting in incomplete sets of vital signs which may limit detection of physiological abnormalities [9,10]. As a result, patients can deteriorate unnoticed, potentially leading to preventable adverse events, failure-to-rescue events and increased hospital costs [11-13].

Attempts to improve recognition of patients at-risk with the implementation of Rapid Response Teams have shown mixed results [14,15]. Successful implementation of a rapid response team critically depends on timely identification of patients at risk ('afferent limb') [16,17]. With the current low monitoring frequency, failure-to-rescue events continue to occur and improvements in terms of patient outcome may require improved recognition of deterioration [13,17,18].

Especially in 'low care' environments such as surgical wards continuous remote monitoring could contribute to earlier recognition of the deteriorating patient [16,19]. Several 'wearable' wireless devices intended for vital signs monitoring recently became available [16]. These devices allow the patient to move freely without the inconvenience of physical attachment to a patient monitor. Such technology combined with appropriate remote monitoring facilities could even allow patients to recover at home by allowing safe discharge earlier after surgery [20,21].

Current wearable sensors are capable of recording heart rate, respiration rate, temperature and movement. Although some wearable sensors have now obtained approval for medical use, uptake within healthcare has been minimal. One reason could be that the validity and reliability has not been studied in relevant clinical environments. Several studies demonstrated the feasibility of wireless monitoring in clinical practice, but comparison with intermittent nurse readings cannot validate the continuous performance of wearable sensors [22-24]. Moreover, these sensors are intended to monitor vital sign trends and as such

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are not designed to deliver 'spot' readings to replace nurse observations. Most accuracy studies of continuous vital signs sensors were obtained under controlled laboratory conditions and for short time periods in volunteers or patients at low risk for developing complications [22,25,26]. Therefore, we cannot translate these findings to high-risk patients at risk for developing vital instability.

We recently studied the potential of a wireless patch sensor for monitoring actual high-risk patients and compared the results with an ICU-grade monitoring system [27]. We hypothesize that wireless sensors can monitor heart rate (HR) and respiratory rate (RR) reliably when compared to a traditional 'wired' reference standard. However, it is unknown how performance differs and how well they perform against a typical 'ICU-grade' patient monitor. Therefore, the objective of this study is to determine whether four systems with different sensing principles can reliably measure HR and RR continuously in high-risk surgical patients.

Materials & Methods

Study design and setting

We performed an observational methods comparison study in which high-risk surgical patients were continuously monitored with two wearable patch sensors (SensiumVitals and HealthPatch), a bed-based mattress sensor (EarlySense) and a patient-worn monitor (Masimo Radius-7) simultaneously during the initial days of recovery at a surgical step-down unit until transition to the traumatology or surgical oncology ward of the University Medical Center Utrecht, the Netherlands. An overview of the measurement setup can be seen in Figure 1. Formal approval for this study was obtained from the local ethical committee (no: 16/062).

Study population

Patients were recruited at the pre-operative screening clinic before surgery or upon admission to the step-down unit. Inclusion criteria were patients from the surgical traumatology or surgical oncology specialty. These patients were considered for enrollment since they represent a high-risk subset of surgical patients that is more prone to deterioration compared to patients on the general ward. Exclusion criteria were patients with bacterial infections requiring barrier nursing, an allergy to skin adhesives, wound or skin lesion near the application site, or patients with a pacemaker or implantable cardioverter defibrillator. After written informed consent was obtained from the patient, the four sensor systems (described in detail below) were applied to the patient and vital signs recording started.
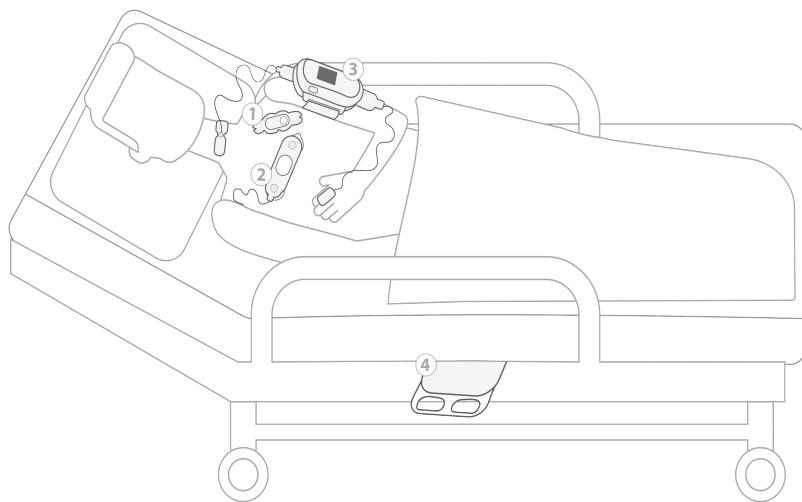
Figure 1. Overview of the measurement setup in patients with two wearable patch sensors placed on the chest (1: HealthPatch, 2: SensiumVitals), a patient-worn monitor connected to a pulse oximeter probe attached to the finger and an acoustic sensor applied in the neck (3: Masimo Radius-7), and a bed-based sensor placed under the patient's mattress (4: EarlySense).

SensiumVitals System (no: 1, wearable 'patch' type sensor)

The SensiumVitals sensor (Sensium Healthcare Ltd, Oxford, UK) is a single-use, lightweight (50 g), wireless and wearable adhesive biosensor that measures HR, RR and axillary temperature every 2 minutes [22]. It is designed to facilitate ambulatory wireless monitoring of patients throughout their hospital ward stay, without the need to change batteries. Measurements are wirelessly transmitted via a low-power radio protocol to hotspots ('bridges' connected to the hospital network) installed throughout the step-down unit, and sent to a central monitoring server. Data was subsequently extracted from the server and saved locally. To guarantee care as usual, healthcare professionals had no access to the data. Study personnel had access to the system to check its functionality.

The patch sensor is applied to the patient's chest by means of two conventional electrocardiogram (ECG) electrodes and measures vital signs continuously (transmitted once every 2 min) up to five days. Although the patch also has a sensor to measure axillary temperature, in this study we only assessed the accuracy and reliability of HR and RR. The sensor internally records HR and RR in a sequential fashion. Every 2 min, a 30 s segment of ECG, followed by a 60 s segment of the respiratory signal is recorded and analyzed. The 30 s period of ECG is recorded and processed to calculate the average HR by analyzing

a single-lead ECG which is pre-processed first to filter the raw ECG signal to minimize noise due to e.g., motion artefacts. The sensor's embedded algorithm rejects the HR signal if it is invalid due to excessive contamination by noise. RR is recorded by impedance pneumography that measures the small impedance changes across the chest as the lungs contract and expand during breathing. The embedded algorithm excludes segments that are corrupted by motion artefacts or other irregular patterns from the calculation of RR values. The manufacturer states an accuracy of ± 2 beats per minute (beats/min), in the range of 30 – 210 beats for HR. The stated accuracy of RR is ± 2 breaths per minute (breaths/min), in the range of 5 – 62 breaths/min.

HealthPatch MD (no: 2, wearable 'patch' type sensor)

The HealthPatch MD (VitalConnect, San Jose, California, USA) is a lightweight (10 g), wireless and wearable adhesive biosensor that measures HR, HR variability, single-lead ECG, RR, skin temperature, body posture and step count. It is designed to facilitate long-term remote monitoring of patients within the hospital setting as well as in the home setting after hospital discharge. Details of the wearable sensor and its system are described in a previous study where the sensor has been tested in a clinical environment [27]. The sensor consists of a disposable patch and a reusable module that needs to be applied on the patient's chest and measures vital signs continuously up to 3 days (4 days if transmission of its single-lead ECG is disabled). The sensor calculates HR using an algorithm which is based on automated detection of QRS complexes from the ECG waveforms. RR is derived from the combined information from three sources: an embedded algorithm uses a weighted average of two characteristics of the ECG signal: (1) QRS amplitude modulation and (2) respiratory sinus arrhythmia; both ECG-derived signals change during inspiration and expiration and the algorithm uses (3) accelerometer data produced by chest movement during respiration [28]. The sensor calculates HR over a period of 10 beats and RR is calculated over a 45 s segment. Both HR and RR are updated every 4s and the manufacturer states an accuracy of ±3 breaths/min, in the range of 4 to 42 breaths for RR. The stated accuracy of HR is ±5 beats/min or 10% (whichever is greater), in the range of 30–200 beats/min.

EarlySense System (no: 3, contactless mattress-sensor)

The EarlySense system (EarlySense Ltd, Ramat Gan, Israel) is a contactless piezoelectric sensor which is placed under the patient's mattress. It connects to an EarlySense bedside monitor that displays HR, RR and body motion with an update time of 60 s as long as the patient remains in bed. The averaging time

to calculate HR is 10 beats and RR is calculated over a segment of 5 breaths. In this study, the EarlySense monitor display was hidden from care professionals. The piezoelectric sensor detects ballistic vibrations of body movements, chest wall movement from respiraton and cardio ballistic movements which are associated with ejection of blood with each heart cycle. The EarlySense system was previously shown to measure HR and RR accurately in patients in ICU settings [29,30]. The manufacturer states an accuracy of ± 5 beats/min or 4% (whichever is greater) in the range of 30 – 170 beats for HR. The stated accuracy of RR is ± 1.5 breaths/min, or 4% (whichever is greater), in the range of 6 – 45 breaths/min.

Masimo Radius-7 (no: 4, patient-worn pulse oximeter and respiratory rate monitor)

Masimo Radius-7 (Masimo Corporation, Irvine, CA, USA) is a patient-worn monitor connected to a pulse oximeter probe attached to the finger for pulse rate and oxygen saturation monitoring and a novel acoustic adhesive sensor applied in the neck (RRa™) for RR monitoring. This acoustic sensor detects upper airway sounds during inhalation and exhalation. Signal processing algorithms convert these acoustic patterns into breathing cycles to calculate RR, whereby it distinguishes breathing patterns from other background noise such as talking, coughing or snoring. The device (a rechargeable module with display) is worn on the upper arm and wirelessly connects via Bluetooth to the base monitor (Masimo 'Root' platform) at the patient's bedside. The sensor records HR over a 30 s epoch and RR over a 60 s segment. These vital signs are updated every second, but stored once per two seconds. With a 12-h battery life, the battery modules must be 'swapped' with a freshly charged device once every nurse shift. For this study, alarms were deactivated and the monitor's display was hidden from care professionals. Ramsay et al. reported high accuracy for RR values of the acoustic monitor when compared with capnography in a study of 33 surgical patients at the post-anesthesia care unit [31]. Another study reported that acoustic monitoring of RR was more accurate when compared with impedance pneumography and frequency modulated continuous wave radar [32]. The manufacturer states an accuracy of ± 3 beats/min (in patients at rest) or ± 5 beats/min (during motion) in the range of 25 – 240 beats for pulse rate. The stated accuracy of RR is ± 1 breath/minute in the range of 4 – 70 breaths/min.

Description of the bedside routine standard

HR and RR of patients were continuously monitored with all four systems as described and simultaneously with a multiparameter bedside monitoring system designed for use in ICUs and operating rooms (XPREZZON, Spacelabs Healthcare,

Snoqualmie, Washington DC, USA) which served as reference monitor. This reference uses ECG for HR detection and measures RR by thoracic impedance pneumography. An ECG epoch of 8 beats is used to calculate HR and it measures RR over a period of 4 breaths. Vital signs are updated every second, but stored once per minute. This reference standard reports an accuracy of ± 3 beats/min or ± 1 % (whichever is greater) in the range of 15 – 300 for HR. The reported accuracy of RR is ± 1 breath/min or ± 5 % (whichever is greater), in the range of 0 – 200.

Signal analysis

Data of the four wireless sensors and the reference system were retrieved in CSV and JSON format and stored in a dedicated local research database. Data were processed using Matlab (The Mathworks, Natick, Massachusetts, USA). Data reports from the reference monitor contained vital signs data sampled once per minute (i.e., one measurement was saved and transmitted every minute). The wireless sensors use different averaging times for HR and RR and send out their data at different update rates. To produce data pairs of the reference standard with each of the wireless sensors for comparison, the update frequency was resampled. Consequently, data of the HealthPatch and data of the Masimo Radius-7 were downsampled to once per minute, which means that one sample per minute of each sensor was retained corresponding to the nearest time point of the reference monitor. To produce paired data points with SensiumVitals (transmitted once every 2 m), data of the reference standard needed to be downsampled from once every minute to once per 2 minutes. The update frequency of EarlySense was unchanged at 1 min.

To ensure alignment between time series, a synchronization method was used based on cross-correlation to estimate the time shift of each index sensor with the reference sensor in order to calculate the number of samples each device needed to be delayed or forwarded in time. This was based on the assumption both signals (e.g., heart rate from the index and reference sensor) were similar in shape, but with different time stamps. After synchronization, a 'moving' median filter with a window of 15 minutes was applied to eliminate movement artefacts.

Outcomes

The primary outcome measure was HR and RR of all wireless sensors as compared with the reference standard. We considered HR and RR to be acceptable for clinical purposes if within ± 10% of the reference standard or ± 5 beats/min or ± 3 breaths/min. A secondary outcome measure was the Clarke Error Grid analysis to quantify the clinical accuracy of HR and RR as compared with the

reference standard. The Clarke Error Grid breaks down a scatterplot of the reference standard and the devices under test in regions A (values within 20% of the reference standard) up to and including region E (values that would lead to reverse treatment decisions of e.g. bradycardia and tachycardia). The regions were defined based on the cut-off boundaries of the Modified Early Warning Score [33]. Another secondary outcome measure was the technical performance of each wireless sensor, which was evaluated by the proportion of total amount of data loss and maximum duration of data loss, defined as gap durations with a maximum length of 5 min, 15 min, 1 hour or 4 hours or longer.

Statistical Analysis

No formal rules for power calculations can be found in literature regarding methods comparison studies where multiple sequential measurements are performed per patient. Therefore, we performed no formal power calculations prior to the study. The sample size was pragmatically based on our desire to at least include 15 adverse events which would allow us to extend validation of the measured sensor values well into the abnormal physiology range.

The data pairs of HR and RR measurements derived from the wireless sensors and the reference sensor were analyzed using the Bland and Altman method for repeated measurements [34] and using mixed effect models as suggested by Myles et al. [35]. The Bland and Altman method was used to account for within-subject variation by correcting for the differences across patients and the variance of differences between the average differences. The bias (mean difference) between the index sensors and reference monitor and the 95% limits of agreement (± 1.96 SD) were determined for both HR and RR data. Furthermore, we calculated the limits of agreement by using a mixed effects model that involves using time as random effect and a random intercept per subject while adjusting for the mean of each subject over time and the mean measurement between each wireless sensor and reference monitor for each measurement occasion. To apply this mixed effect model, we checked that the variance of the repeated measurements for each patient was independent of the mean of the repeated measurements. This random effect model of Myles was suggested as modification for handling repeated measurements [35].

In addition, a Clarke Error Grid analysis was conducted to specify clinical accuracy of the wireless sensors against the reference standard and to study the potential consequences for treatment decisions [36]. This was expressed as the percentage of data representing adequate and inadequate treatment decisions. Technical

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performance was analyzed by the duration of data loss and the total amount of data loss. Duration of data loss with a maximum length of 4 min, 15 min, 60 min or longer than 4 hours were identified to evaluate the potential of wireless monitoring. The analyses were conducted using Matlab version 2017b (The Mathworks, Inc., Natick, Massachusetts, USA).

To evaluate the *trending ability* of heart rate and respiratory rate of the wireless sensors, we created four-quadrant plots and calculated the concordance rate for each of the wireless sensors using an exclusion zone of 1 beat/min for heart rate and 1 breath/min for respiratory rate [37].

Results

From February to September 2017, a total of 31 high-risk surgical patients entered the study of which 25 were monitored on the step-down unit. The other 6 patients were only monitored at the surgical ward, because they were immediately transferred from ICU to the ward and bypassed the step-down unit, or the time to conduct measurements at the step-down unit was too short. In total, 720 hours of vital signs monitoring on the step-down unit with all wireless sensors attached were available, with a median duration of 19 hours per patient (min: 21 minutes, max: 111 hours). Except for three patients, who were not monitored with the HealthPatch sensor, due to shortage of these sensors. Table 1 summarizes patient characteristics.

Table 1. Patient characteristics (N=25)

Gender	Female	9 (36)
n (%)	Male	16 (64)
Age (years)		62 [51-71]
median [IQR]		
BMI (kg/m2)*		27 [25-30]
median [IQR]		
Specialty	Surgical Gastro-intestinal Oncology	14 (56)
n (%)	Traumatology	11 (44)
Admission diagnosis	Esophagectomy	10 (32)
	Herniation colon	1 (4)
	Hemihepatectomy	1 (4)
	Enucleation of neuroendocrine tumor	1 (4)
	Surgery for liposarcoma	1 (4)
	Trauma (pneumothorax, hemothorax, multiple rib fractures, cruris fracture)	11 (44)

Table 1. Continued.

ASA physical status	ASA 1 - 2	19 (76)
n (%)	ASA 3 - 4	6 (24)
Comorbidities	Hypertension	4 (16)
n (%)	Cardiovascular disease	2 (8)
	COPD	3 (12)
	Diabetes	2 (8)
Length of hospital stay (days)		13 [11-20]
median [IQR]		
Readmission to hospital within 30 days		2 (8)
n (%)		

* BMI of one patient was missing
IQR: Interquartile range

Heart rate

Table 2 shows bias and precison (95% limits of agreement) from comparisons between the four wireless sensors and the reference standard after applying a 'moving' median filter of 15 minutes. Bias and the 95% limits of agreement derived from the mixed effect models for HR of the SensiumVitals, HealthPatch, EarlySense and Masimo Radius-7 were all within the predefined acceptable range. The 95% limits of agreement as calculated with the Bland Altman method showed wider limits of agreement for all sensors. The HealthPatch showed the narrowest limits of agreement as can be seen in the Bland and Altman plots of Figure 2A-D, with limits of agreement from the Bland Altman method in black, and from the mixed effect models in red. Although HR derived with the Masimo Radius-7 sensor was accurate for sinus rhythm. After visual inspection of the measurements, substantial variability of HR of the Masimo Radius-7 sensor was observed during episodes of atrial fibrillation in 5 patients.

Respiratory rate

The mean difference and limits of agreement derived from the mixed effect models for RR of the SensiumVitals, EarlySense and Masimo Radius-7 were all within the predefined accepted range as shown in Table 2. The HealthPatch overestimated RR, with a mean difference of 4.4 breaths/min and with wide levels of agreement of -4.4 to 13.3 breaths/min. The 95% limits of agreement calculated from the Bland and Altman method showed wider limits of agreement for all sensors. EarlySense showed the narrowest limits of agreement for RR. Figure 3A-D illustrates the Bland and Altman plots.

Table 2. Bland Altman analysis for heart rate and respiratory rate from the wireless sensors versus the reference monitor

	No of measurement pairs	No of patients	Bias	Lower 95% LoA BA[a]	Upper 95% LoA BA[a]	Lower 95% LoA MEM[b]	Upper 95% LoA MEM[b]
Heart Rate							
SensiumVitals	16,917	25	1.0	-14.6	16.7	-6.3	8.4
HealthPatch	29,619	22	1.3	-4.1	6.9	-0.5	3.3
EarlySense	29,470	25	-1.4	-13.2	10.4	-5.1	2.3
Masimo	34,992	25	-0.4	-11.9	11.0	-4.0	3.1
Respiratory Rate							
SensiumVitals	17,595	25	-0.8	-8.5	6.9	-7.4	5.6
HealthPatch	29,135	22	4.4	-5.8	14.7	-4.4	13.3
EarlySense	27,921	25	0.4	-5.6	6.4	-3.9	4.7
Masimo	33,032	25	0.2	-6.6	6.3	-4.7	4.4

[a] LoA = limits of agreement
[a] BA = Bland & Altman method
[b] MEM = Mixed Effect Models
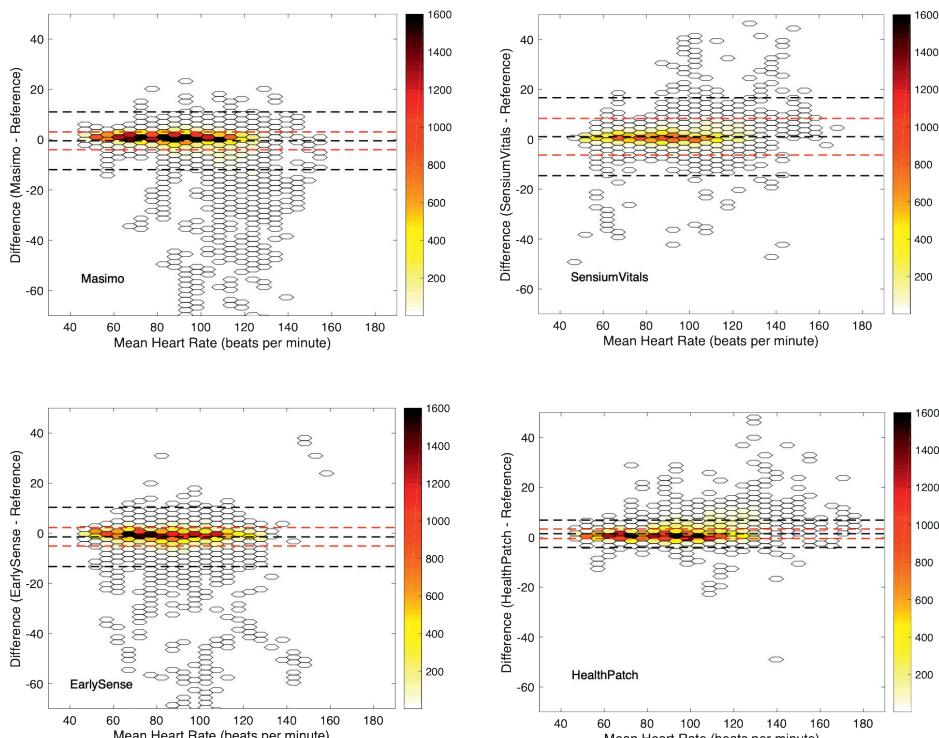
Figure 2. Bland and Altman plots of heart rate for Masimo Radius-7, SensiumVitals, EarlySense, and HealthPatch. Limits of agreement from the Bland–Altman method in black, and from mixed effects models in red.
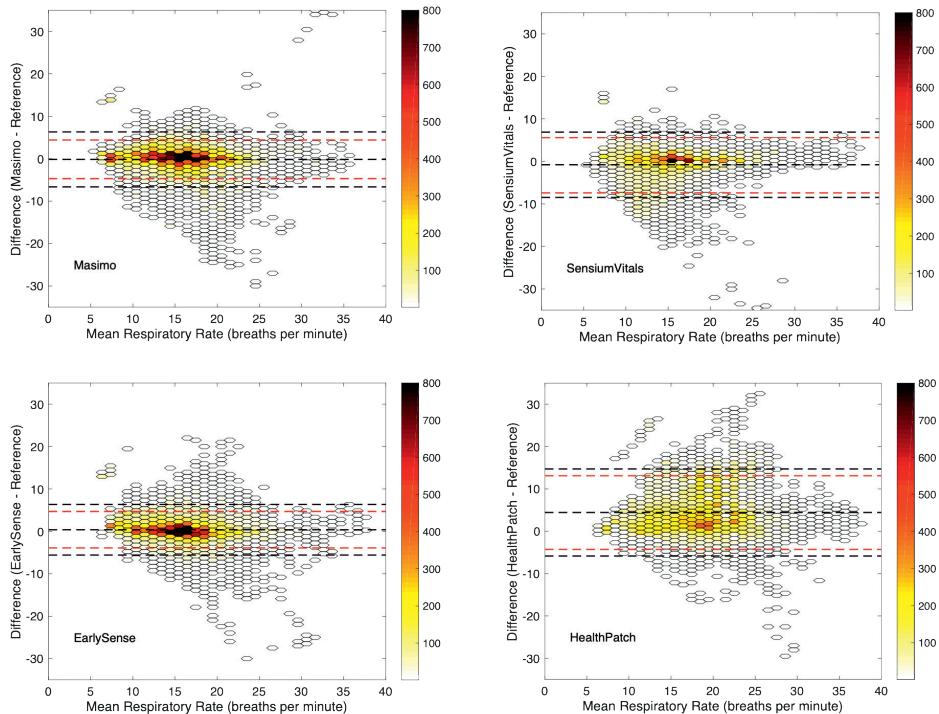
Figure 3. Bland and Altman plots of respiratory rate for Masimo Radius-7, SensiumVitals, EarlySense, and HealthPatch. Limits of agreement from the Bland–Altman method in black, and from mixed effects models in red.

Clinical accuracy of the wireless sensors

The Clarke Error Grid analyses of HR and RR of each wireless sensor are plotted in Figure 4A-D and Figure 5A-D. The percentage of data pairs in the regions A-E are shown in Table 3. Region A or B, respectively indicates, within 20% of the reference standard, or outside 20% of the reference but not leading to unnecessary or wrong treatment. These results show that adequate treatment decisions regarding changes in heart rate (zone A or B) would have been taken in 99.4%, 100%, 99.5% and 99.5% with the SensiumVitals, HealthPatch, EarlySense and Masimo Radius-7 respectively. None of the HealthPatch HR measurements and only a very few (<= 0.5%) of the HR measurements of Masimo Radius-7, EarlySense and SensiumVitals were within region C, D or E, suggesting that very few measurements would lead to failure to treat, unnecessary treatment or confusion between bradycardia and tachycardia.

For RR, adequate treatment decisions would have been 92.7%, 77.3%, 96.6% and 96.3% with the SensiumVitals, HealthPatch, EarlySense and Masimo Radius-7 respectively. A number of RR measurements (> 10%) of the HealthPatch sensor were within region C, D or E, indicating a potentially dangerous failure to apply the right treatment.

Four-quadrant plots showing the trending ability of Δ heart rate and Δ respiratory rate (i.e, difference between consecutively obtained RR and HR values) for both the wearable sensors and reference standard are shown in a density plot as can be found in Appendix 1.
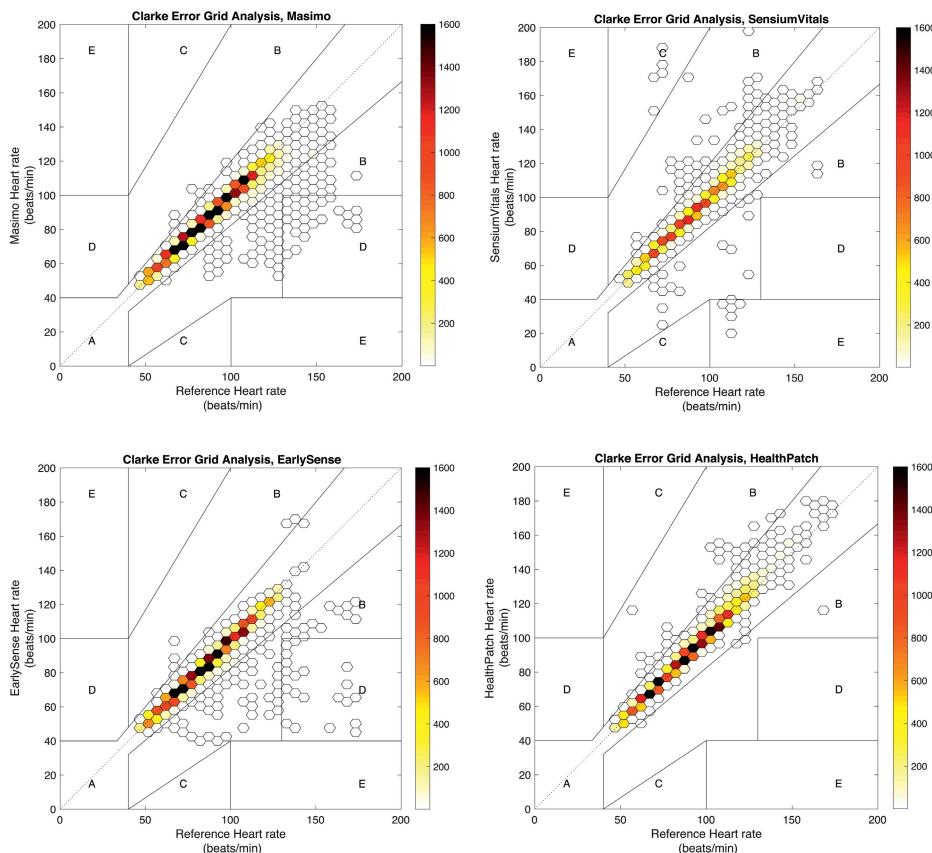
Figure 4. Clarke Error Grid analysis to quantify clinical accuracy of the heart rate measurements with the Masimo Radius-7 (A), SensiumVitals (B), EarlySense (C), and HealthPatch (D) as compared with the reference standard. The colored dots are measurement pairs each superim- posed on the Error Grid boundaries, where the color intensity is proportional to the number of observations. Region A encloses points within 20% of the reference monitor; region B contains points outside 20% of the reference, but not leading to unnecessary treatment.

Region C contains points leading to unnecessary treatment, region D indicates a potentially dangerous failure to detect bradycardia or tachycardia, and region E represents points where events are confused (e.g., bradycardia with tachycardia).

Figure 5. Clarke Error Grid analysis to quantify clinical accuracy of the respiratory rate measurements with the Masimo Radius-7 (A), SensiumVitals (B), EarlySense (C), and HealthPatch (D) as compared with the reference standard. The colored dots are measurement pairs each superimposed on the Error Grid boundaries, where the color intensity is proportional to the number of observations. Region A encloses points within 20% of the reference monitor; region B contains points outside 20% of the reference, but not leading to unnecessary treatment. Region C contains points leading to unnecessary treatment, region D indicates a potentially dangerous failure to detect bradypnoea or tachypnoea, and region E represents points where events are confused (e.g., bradypnoea with tachypnoea).

Table 3. Clarke error grid analysis to quantify clinical accuracy of HR and RR of all wireless sensors

|	Zone A	Zone B	Zone C	Zone D	Zone E	Zone A + B
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Heart Rate						
Masimo	34,645 (99.0)	166. (0.5)	0 (0)	181 (0.5)	0 (0)	34,811 (99.5)
EarlySense	29,123 (98.8)	206 (0.7)	19 (0.1)	122 (0.4)	0 (0)	29,329 (99.5)
HealthPatch	29,576 (99.9)	39 (0.1)	4 (0)	0 (0)	0 (0)	29,615 (100)
SensiumVitals	16,682 (98.6)	139 (0.8)	54 (0.3)	5 (0)	37 (0.2)	16,821 (99.4)
Respiratory Rate						
Masimo	27,198 (82.3)	4,610 (14.0)	235 (0.7)	907 (2.7)	82 (0.3)	31,808 (96.3)
EarlySense	22,417 (80.3)	4,597 (16.5)	302 (1.1)	597 (2.1)	8 (0)	27,014 (96.6)
HealthPatch	14,179 (48.7)	8,344 (28.6)	5,631 (19.3)	453 (1.5)	528 (1.8)	22,523 (77.3)
SensiumVitals	13,003 (74.0)	3,314 (18.7)	758 (4.3)	384 (2.2)	136 (0.7)	16,317 (92.7)

Technical performance

Data loss of HR measurements was 12.9% (83 of 633 h), 12.3% (79 of 640 h), 27.5% (182 of 664 h) and 6.5% (47 of 727 h) for SensiumVitals, HealthPatch, EarlySense and Masimo Radius-7 respectively. In addition, available HR data from the reference standard was not continuously available either (data loss of 154 of 727 h; 21.2%). For RR, data loss was 34.0% (122 of 359 h), 13.1% (83 of 633 h), 37.9% (250 of 659 h) and 12.8% (92 of 720 h) for SensiumVitals, HealthPatch, EarlySense and Masimo Radius-7 respectively. From the reference standard data loss of RR measurements was 20.6% (148 of 720 h). Figure 6 shows the percentage of epochs without data divided over gaps of data loss with a maximum length of 5 min, 15 min, 1 hour, 4 hours or longer than 4 hours. More than 90% of the gap durations were not longer than 15 minutes for both HR and RR, with the majority of gaps < 5 minutes. Except for HealthPatch where 84% of the gaps of HR data were below 15 minutes and for Masimo Radius-7 where 89% of the gaps for RR were under 15 minutes.
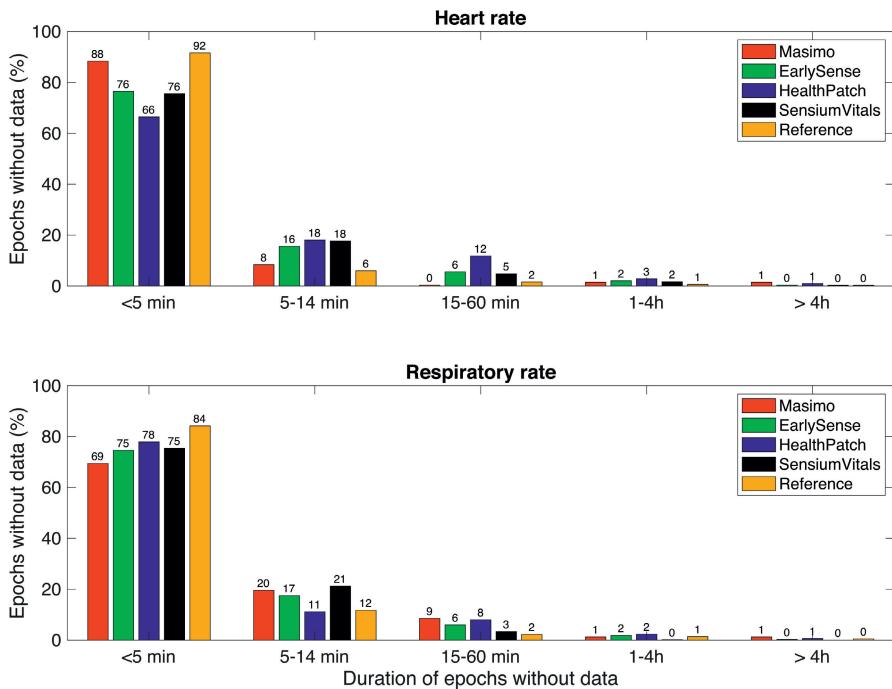
Figure 6. Overview of epochs without data (%) divided over gaps of data loss with a maximum length of 5 min, 15 min, 1 h, 4 h, or longer than 4 h for each sensor. The EarlySense data contain epochs without data during bed exits and mobilization.

Table 4. Overall amount of data loss of each sensor, measured as percentage of total monitoring time in minutes.

	Percentage of total data loss n (%)[b]
Heart Rate	
SensiumVitals	2,776 (12.9)
HealthPatch	4,726 (12.3)
EarlySense [a]	10,939 (27.5)
Masimo	2,830 (6.5)
Reference standard	9,232 (21.2)
Respiratory Rate	
SensiumVitals	7,338 (34.0)
HealthPatch	4,986 (13.1)
EarlySense [a]	14,999 (37.9)
Masimo	5,524 (12.8)
Reference standard	8,891 (20.6)

[a] No data available during bed exits and mobilization
[b] Expected data loss was not excluded (e.g., sensors that were temporarily disconnected during certain diagnostic procedures)

Discussion

We studied the performance of two wearable patch sensors, a patient-worn monitor and a contactless mattress sensor to measure HR and RR continuously in high-risk surgical patients. The results show that these sensors can accurately measure HR, with the highest precision for the HealthPatch sensor. For RR, the accuracies of Masimo Radius-7, EarlySense and SensiumVitals were within our predefined acceptable range. In contrast, the HealthPatch tended to overestimate RR. Furthermore, clinical accuracy of all sensors for HR was nearly 100%. EarlySense had the lowest percentage of RR measurements in regions D (failure to detect bradypnea/tachypnea) and E (opposite treatment). The wireless systems provided data more than 62% of time for RR and more than 73% of time for HR. Surprisingly, the wired reference system provided data only 79% of time for both HR and RR, which is lower than most wireless sensor systems. One possible explanation is pull on ECG electrodes from patient movement. Available HR and RR data was lowest for the bed-based EarlySense, since there are no data when the patient is not in bed, for instance during mobilization.

We recently reported on the accuracy of Healthpatch [27], but including a wider range of wearable wireless sensors in this study provided a fuller understanding of the differences in reliability. Until now, most accuracy studies were obtained under laboratory conditions, or with low-risk patients for a limited time [22,25,26,28]. Comparison of RR from Masimo Radius-7 and capnography showed high accuracy at the post-anesthesia care unit. Two recent studies reported high accuracy for Masimo Radius-7 RR when compared with capnography and impedance pneumography [31,32]. The EarlySense system can track HR and RR accurately in ICU patients [29], although data were obtained during supervised conditions. Other studies used nurse-recorded vital signs observations as reference method. Granholm et al. [24] mentioned an unacceptable lack of agreement between SensiumVitals and nurse readings, while Weenk et al. [23] reported that HealthPatch recordings were in agreement with nurse measurements. Although such studies hint at the potential of wireless monitoring in clinical practice, comparison with nurse observations cannot reliably indicate (continuous) performance of wearable sensors. First, nurses have digit preferences for RR readings and their approximations deviate from the actual RR [38,39]. Second, nurse readings were evaluated against 'spot' measurements, which is outside the intended scope of continuous monitoring. Finally, continuous vital signs cannot be validated in-between nurse observations. In the present study,

HR and RR were measured continuously with both the index sensors and a reference monitor in a high-risk clinical setting.

The results of the present study confirm that the wireless devices provide similar monitoring accuracy as the wired reference standard. However, each system has specific strengths and drawbacks. Both 'patch type' sensors use ECG to derive HR, which was highly accurate. The Masimo Radius-7 uses photoplethysmography from the finger probe to derive HR, which was accurate, except during atrial fibrillation with rapid ventricular rate where it underestimated actual ventricular rate. The bed-based EarlySense monitor estimates HR with ballistocardiography and, as a result, it also underestimated HR during atrial fibrillation. For all devices, RR was clearly the more difficult vital sign to measure. The HealthPatch sensor overestimated RR, whereas respiratory rate estimates from the SensiumVitals patch were more robust.

Although the reference standard used in the present study is part of our hospital-wide ICU monitoring system, and thus clinically relevant, its thoracic impedance measurement cannot be considered a true 'gold' standard for RR monitoring, and observed RR shows wide variations in patients who are moving and talking [40]. An unknown part of the measurement error is therefore potentially related to deficiencies of the reference standard, rather than the wireless sensors. To account for this, we also derived the limits of agreement with mixed effect models which adds the mean of each patient over time and the mean measurement of each measurement pair as explanatory variable. These results showed that the limits of agreement were reduced for both HR and RR of all four sensors under test, suggesting that RR derived with the reference differs from the actual RR. Although we considered using capnography as reference standard instead of thoracic impedance for RR, in pilot tests we found that unsupervised capnography in spontaneously breathing patients was prone to frequent sensor malposition, high amounts of data loss and poor patient acceptance [41]. Capnography as a reference standard for RR is only feasible for shorter periods of time when a research assistant is continuously present to observe and maintain correct sensor position.

We considered HR and RR to be acceptable for clinical purposes if within ± 10% of the reference standard or ± 5 beats/min or ± 3 breaths/min. These limits may be considered 'wide' during controlled conditions, but not during unsupervised monitoring of patients who were at times moving and talking. However, guidelines for acceptable limits of agreement with continuous vital

signs monitoring do not yet exist. It may be clinically desirable to redefine acceptable accuracy limits depending on the value of the vital sign measured, for example, for very high respiratory rates it is less relevant if the RR is 32 or 35 breaths/min. However, for low respiratory rates it is critically important to know whether a patient's RR is 8 or 5 breaths/min.

When interpreting the findings of this study some limitations should be taken into account. First, the observation time available for agreement analysis varied per patient. This was due to variability in length of stay and whether patient participation started before surgery or upon admission. However, given the large amount of monitored time available, we believe we can draw valid inferences regarding the reliability of the different sensors. A second limitation is our inability to assess the exact amount of data loss in the EarlySense system, because no data were available on the number and duration of bed exits, which overestimated data loss. Although the accuracy of available EarlySense HR and RR data was good, it is important to realize that during periods of mobilization there is no indication of a patient's vital status.

Data loss was highest for RR from the SensiumVitals sensor; however, a 66% available data rate still provides much more information regarding the patient's vital status than the current frequency of nurse readings on the ward. This data loss may be a result of the 'conservative' algorithm used, which strictly rejects potentially invalid RR readings in an attempt to reduce the incidence of false alarms, e.g. from motion artefacts [22]. Moreover, more than 90% of episodes with data loss did not exceed 15 minutes, which means that with a 15 min moving median filter used in the present study, still two-thirds of values are transmitted and brief transmission loss would not result in false alarms. Surprisingly, data loss for HR and RR data from the reference monitor was > 20%, possibly due to pull on ECG electrodes. In such cases wireless HR monitoring might even outperform conventional wired systems.

We opted to use a 'moving' median filter over 15 min data epochs with an update rate once every minute to eliminate HR and RR outliers resulting from patient motion. Applying such filtering, however, reduces the ability to detect sudden changes in vital signs, for example apnea or cardiac arrest. The current first-generation of wearable devices are not designed to substitute ICU-grade monitoring systems for continuous monitoring. Their intended use is to identify abnormal trends in physiology in order to get the right care to the right patient at the right time. Consequently, eliminating spurious vital signs outliers at the

expense of real-time monitoring might be a necessary trade-off. This approach minimizes false-positive alerts, which is paramount to avoid alarm fatigue and direct nurses to only go see patients who are in need of extra observation. This is relevant when remote patient monitoring solutions are deployed on a general surgical ward, where nurse-to-patient ratios are much lower, and in the home setting with only limited (remote) supervision.

The potential benefits of continuous remote wireless patient monitoring are increasingly recognized [16,42-44]. A recent review by Downey et al. [45] concluded that continuous monitoring outside critical care settings is feasible and may show patient benefits in terms of improved outcomes and cost efficiency. Another review suggested that implementation of remote monitoring with automated notifications increased involvement of ward physicians, rather than increased rapid response teams activation [43]. Nonetheless, large well-controlled studies in high-risk populations are needed to obtain evidence of the impact of remote monitoring on postoperative outcomes. Particular emphasis in future studies should be on the unintended consequences of remote monitoring, such as the risk of reduced patient contact and inappropriate consultation of end-users during the introduction of new technology [46].

In conclusion, the tested wearable devices accurately represented heart rate. Respiratory rate was clearly harder to measure, but the devices were accurate enough to identify abnormal patterns in respiratory rate. None of the tested devices is designed to substitute continuous ICU-grade monitoring systems, and our data suggest they cannot be used as such. However, wireless wearable vital signs sensors could become valuable tools to reduce failure-to-rescue events within patients outside of high-care facilities.

3

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Appendix 1
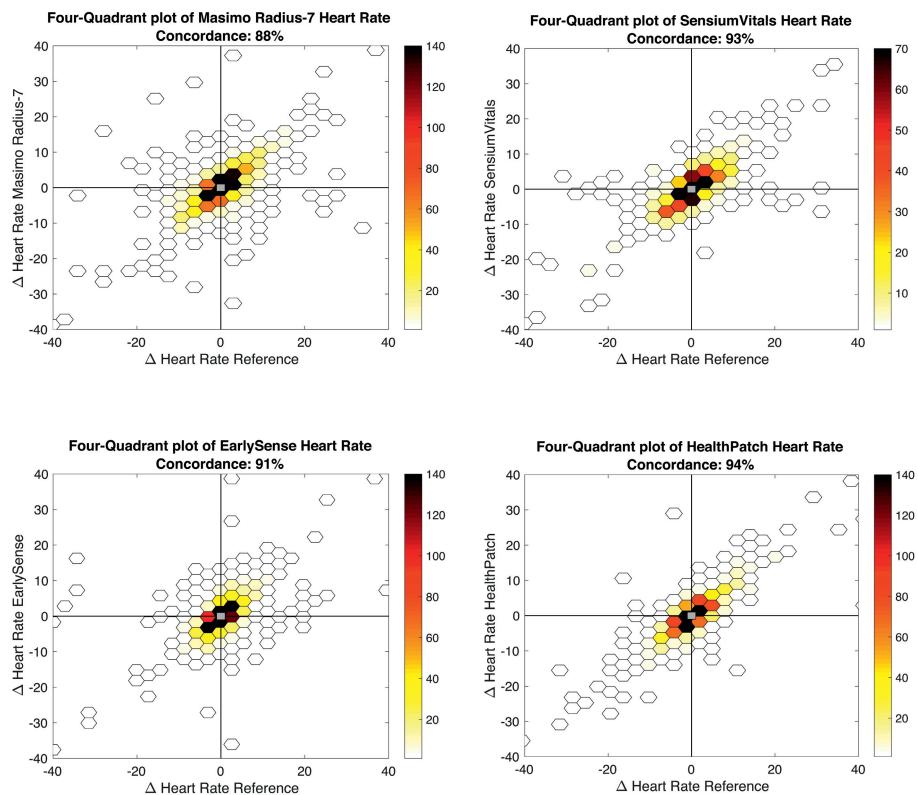
Figure Appendix 1. Four-quadrant plot showing the Δ heart rate values for both the reference standard and the wearable sensors. The values on the horizontal axis refer to Δ heart rate values of the reference; the vertical axis refers to the Δ heart rate values of the studied sensors.

Appendix 2
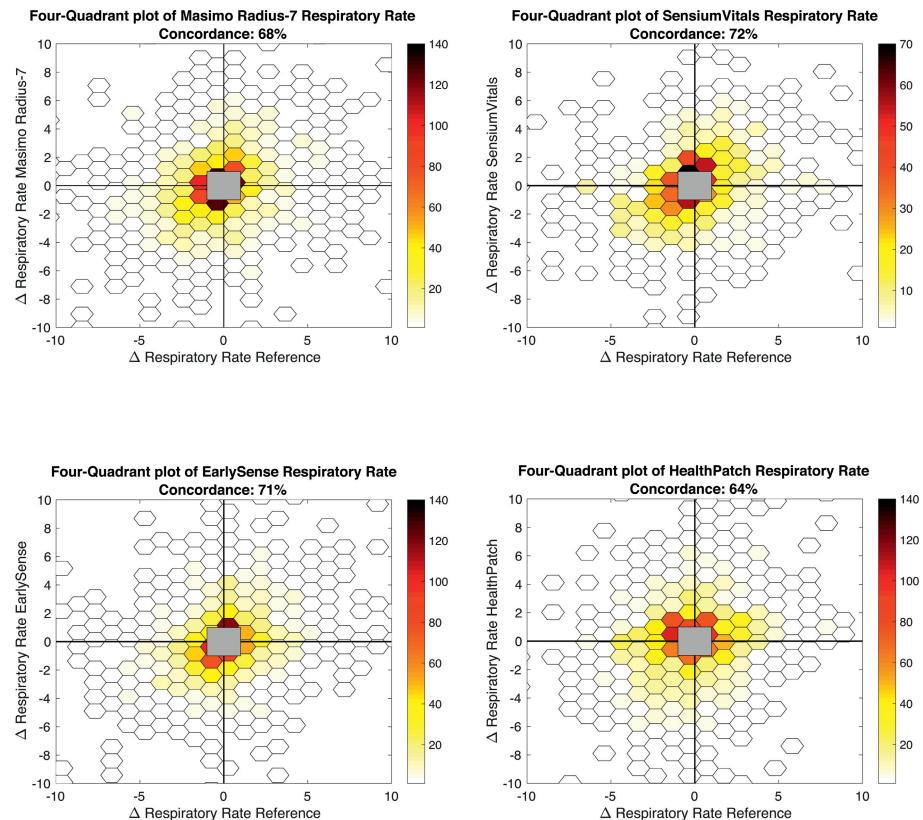
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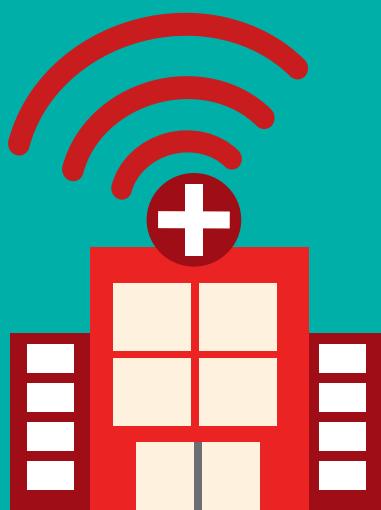
Chapter 4

Are current wireless monitoring systems capable of detecting adverse events in high-risk surgical patients? A descriptive study

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Abstract

Background: Adverse events are common in high-risk surgical patients, but early detection is difficult. Recent innovations have resulted in wireless and 'wearable' sensors, which may capture patient deterioration at an early stage, but little is known regarding their ability to timely detect events. The objective of this study is to describe the ability of currently available wireless sensors to detect adverse events in high-risk patients.

Methods: A descriptive analysis was performed of all vital signs trend data obtained during an observational comparison study of wearable sensors for vital signs monitoring in high-risk surgical patients during the initial days of recovery at a surgical step-down unit (SDU) and subsequent traumatology or surgical oncology ward. Heart rate (HR), respiratory rate (RR) and oxygen saturation (SpO$_2$) were continuously recorded. Vital sign trend patterns of patients that developed adverse events were described and compared to vital sign recordings of patients without occurrence of adverse events. Two wearable patch sensors were used (SensiumVitals and HealthPatch), a bed-based mattress sensor (EarlySense) and a patient-worn monitor (Masimo Radius-7).

Results: Twenty adverse events occurred in 11 of the 31 patients included. Atrial fibrillation (AF) was most common (20%). The onset of AF was recognizable as a sudden increase in HR in all recordings, and all patients with new-onset AF after esophagectomy developed other postoperative complications. Patients who developed respiratory insufficiency showed an increase in RR and a decrease in SpO$_2$, but an increase in HR was not always visible. In patients without adverse events, temporary periods of high HR and RR are observed as well, but these were transient and less frequent.

Conclusions: Current systems for remote wireless patient monitoring on the ward are capable of detecting abnormalities in vital sign patterns in patients who develop adverse events. Remote patient monitoring may have potential to improve patient safety by generating early warnings for deterioration to nursing staff.

Introduction

Adverse events are common in high-risk patients within the hospital. In surgical patients, the incidence of complications after major surgery is reported between 17 and 44 percent, with a significant associated mortality [1-3]. Obviously, complications have a negative effect on patient health and outcome, but a delay in detection of adverse events frequently aggravates the patient's condition. In the majority of adverse events, early signs of deterioration are present up to 48 h prior to admission to the Intensive Care Unit (ICU) [4-7]. The poor condition of patients upon arrival in the ICU reflects such a delay [8,9]. Early recognition of adverse events could lead to better outcomes, as adequate treatment of complications can be initiated before failure-to-rescue events occur [10,11].

During rounds on the ward vital signs are usually measured and documented by nurses. The frequency of measurements is increased when this is deemed necessary and in case of aberrant signs the medical staff is informed. Although nurses have been manually checking patient's vital signs dating back to the 19th century, this routine monitoring practice has several potential flaws. First, the frequency of monitoring is low, generally once per nurse shift. Second, relevant changes in vital signs may remain undetected, specifically when the changes are subtle or still within the normal range of physiology. Third, compliance from nurses to vital sign monitoring protocols is often poor, resulting too often in incomplete or incorrect documentation of data [12-14]. These drawbacks of monitoring are in part responsible for the delay in detection of adverse events or complications.

With the introduction of wearable sensors that allow wireless continuous vital signs monitoring, substantial improvement in patient safety might be achieved [15]. Various manufacturers recently developed systems for this purpose, some of which are FDA or CE approved, claiming to enhance patient safety. Ideally, wireless vital signs monitoring should be reliable, unobtrusive, and provide input to a clinical decision support system that alerts nursing staff early in case of patient deterioration. Importantly, the false alarm rate should be as low as possible in order to prevent 'alarm fatigue', a dangerous phenomenon which results in desensitization to alarms and missed alarms. In particular, such systems might benefit from the use of 'intelligent' alarms to identify relevant changes in physiological state when an adverse event develops. To date, however, no system meets all these requirements.

4

We recently critically validated the accuracy of four wireless systems with different sensing principles to study whether they can reliably measure heart rate and respiratory rate continuously in high-risk surgical patients [16]. While validating these sensors, several adverse events occurred in some of these patients. In this overview we aim to describe the ability of currently available sensors to detect vital signs changes prior to and during these events in a group of high-risk surgical patients.

Materials and Methods

Study design and Setting

We performed a descriptive analysis of all vital signs trend data obtained during an observational methods comparison study of wearable sensors for vital signs monitoring. A subset of patients developed adverse events during these vital signs recordings. In this study, vital sign trend patterns of patients with adverse events are described in more detail and compared to vital sign recordings of patients without occurrence of adverse events.

Heart rate and respiratory rate were continuously recorded in high-risk surgical patients with two wearable patch sensors (SensiumVitals: Sensium Healthcare Ltd, Oxford, UK, and HealthPatch: VitalConnect, California San Jose, CA), a bed-based mattress sensor (EarlySense; EarlySense Ltd, Ramat Gan, Israel) and a patient-worn monitor (Masimo Radius-7: Masimo Corporation, Irvine, CA, USA) simultaneously during the initial days of recovery at a surgical step-down unit (SDU) and subsequent stay on the traumatology or surgical oncology ward of the University Medical Centre Utrecht, the Netherlands. Besides heart and respiratory rate, oxygen saturation was continuously recorded with a SpO_2 finger probe (Masimo Radius-7). No alarms were generated and sent to nurses. A description and image of each sensor is shown in Table 1 and Figure 1 respectively. Formal approval for this study was obtained from the local ethical committee (nr 16/062).

Study population

For elective cases between February and September 2017, consecutive patients scheduled for major surgery with an indication for postoperative monitoring at the step-down unit were asked to participate at the pre-operative screening clinic. Acute cases were asked for participation upon admission to the step-down unit. These patients were considered for enrolment because they represent a population that is more prone for deterioration as compared to patients on the general ward only. Patients with an implantable cardiac device, patients who

were allergic for any adhesives, or who had a wound or irritation near the sensor application site on the thorax, were excluded. After written informed consent was obtained from the patient, the four sensor systems (table 1) were applied simultaneously to the patient and vital signs recording started.

Table 1. Overview of wireless monitoring solutions

Sensor (manufacturer)	Sensor type	Vital signs measured	Update rate vital signs
Masimo Radius-7 (Masimo Corporation, Irvine, CA, USA)	Patient-worn monitor connected to a pulse oximeter and acoustic adhesive sensor in the neck (RRa)	Heart rate (pulse rate) Respiration rate Saturation	Every 2 sec (storage)
SensiumVitals (Sensium Healthcare Ltd, Oxford, UK)[a]	Wireless adhesive patch sensor on chest	Heart rate Respiration rate	Every 120 sec
HealthPatch MD (VitalConnect, San Jose, California, USA)[b]	Wireless adhesive patch sensor on chest	Heart rate Respiration rate	Every 4 sec
EarlySense system (EarlySense Ltd, Ramat Gan, Israel)	Contactless piezoelectric sensor under the patient's mattress	Heart rate Respiration rate	Every 60 sec

[a] The Sensium system measures axillary temperature too
[b] The HealthPatch MD measures skin temperature too

Data selection and analysis

All vital sign recordings were divided into two groups: recordings of patients that developed adverse events and patients without occurrence of adverse events. For both groups, vital sign trend patterns were compared and described in detail. A median filter over a 120 s period was applied to the raw sensor data of Masimo Radius-7, HealthPatch MD and the EarlySense system to be able to evaluate the trend data among all sensors with the same update rate. The update rate of SensiumVitals was unchanged (see Table 1). Adverse events were defined as any complication that may or may not have been preventable which required intervention.

We summarized and evaluated all adverse events. An example of this would be the description of vital sign patterns during periods of atrial fibrillation or an anastomotic leak. Furthermore, we studied to what extent such vital sign patterns were observable in patients who did not develop adverse events. All vital sign trends were visualized using Matlab R2017b (The Mathworks, Natick, Massachusetts, USA).

A.

B.

C.

D.

Figure 1. Overview of the four wearable sensors: (A) Masimo Radius-7; (B) SensiumVitals; (C) HealthPatch MD; (D) EarlySense system.

Results

During the study period, 31 patients were included for continuous vital signs recording with wearable sensors. Twenty adverse events occurred in 11 patients, of which 9 (45%) during SDU stay and 11 (55%) at the surgical ward. Six out of these 11 patients developed multiple adverse events (two events; n=4 or three events; n=2). In total, 2607 hours of vital signs recording were available for analysis, with a median duration of 88 hours per patient. Table 2 summarizes patient characteristics. An overview of adverse events is summarized in Table 3.

Table 2. Patient characteristics (N = 31)

Male, *n* (%)	21 (68)
Age (years) Median (IQR)	62 (20)
Specialty	
Surgical oncology, *n* (%)	16 (52)
Trauma, *n* (%)	15 (48)
Comorbidities	
Hypertension, *n* (%)	5 (16)
Diabetes, *n* (%)	3 (1)
COPD, *n* (%)	3 (10)
Cardiovascular disease, *n* (%)	2 (6)
Length of stay (days) *Median (IQR)*	12 (9)
Readmission within 30 days , *n* (%)	2 (6)
Length of vital sign recording (hours) *Median (IQR)*	88 (74)

Table 3. Overview adverse events

Type AE	n (%)
Atrial fibrillation	4 (20)
Pneumonia	4 (20)
Pneumothorax	3 (15)
Anastomotic leak	2 (10)
Gastroparesis	2 (10)
Pulmonary Embolism	1 (5)
Atelectasis	1 (5)
Diaphragmatic hernia	1 (5)
Pancreatic leak	1 (5)
Chyle leak	1 (5)
Total	20
Number of AEs at the SDU	9 (45)
Number of AEs at the ward	11 (55)
Other	
SDU readmission	3 (16)
ICU readmission	1 (5)

4

Descriptive analysis of vital signs recordings in patients who developed one or more adverse events

Figure 2 shows HR, RR and SpO$_2$ measurements during the fifth and sixth day postoperatively of a 63-year-old male patient after esophagectomy at the SDU. Three events occurred before the patient was readmitted to the ICU. The first event shows a sudden HR increase on March 8th, diagnosed as new-onset atrial fibrillation, which started after patient mobilization. The next morning, on March 9th, this patient developed a pneumothorax (second event) and anastomotic leak (third event); he rapidly developed respiratory insufficiency and was diagnosed with sepsis, followed by urgent ICU readmission. The following changes in vital signs can be seen in Figure 2, before these two events were diagnosed: a slowly increasing HR from 100 to 130 bpm, an increasing RR from 18 to > 35 brpm and a more subtle decrease in oxygen saturation, from 97% to 93%. Figure 2 also illustrates that both Masimo Radius-7 and the EarlySense system underestimate HR during periods of AF.
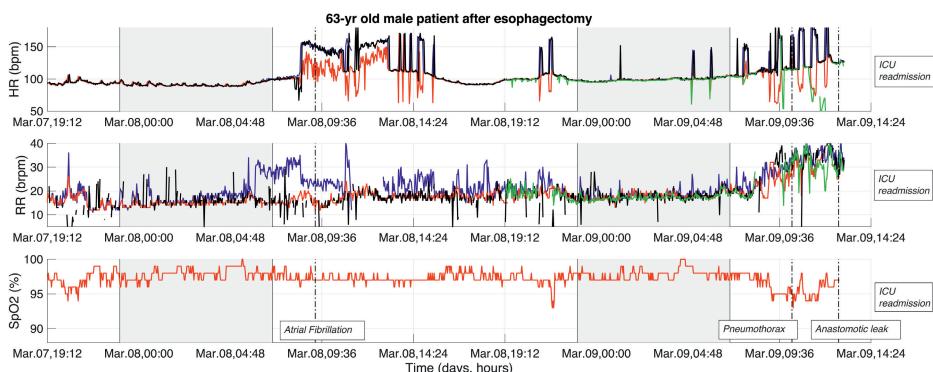
Figure 2. Example of a patient who developed adverse events, while vital signs were recorded continuously on the surgical ward with the two wireless patch sensors (SensiumVitals: black, HealthPatch MD: blue), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas.

Figure 3 shows the vital sign trends of a 68-year old male patient after esophagectomy from the 2nd to 8th day postoperatively. In the afternoon of June 18th, the patient complained of chest pain and acute dyspnea after. Subsequently, pulmonary embolism was diagnosed. In the hours before and after this event, an increase in HR from 75 to 110 bpm was seen and a more subtle increase in RR from 14 to 21 brpm. Oxygen saturation frequently decreased below 90% (Figure 3). In the evening of June 19th, the nurse palpated the pulse of the patient and was unsure whether it was irregular. A subsequent ECG did not show AF. The diagnosis of new-onset AF was not confirmed until another ECG early in the morning of

June 21th. In addition, the patient also complained of intolerable epigastric pain. Subsequently, a pancreatic fistula was diagnosed.

Although new-onset AF was not diagnosed before June 21th, the HR pattern frequently showed sudden increases or decreases of HR (Figure 3). In addition, both Masimo Radius-7 and EarlySense underestimate the ventricular rate during rapid AF.
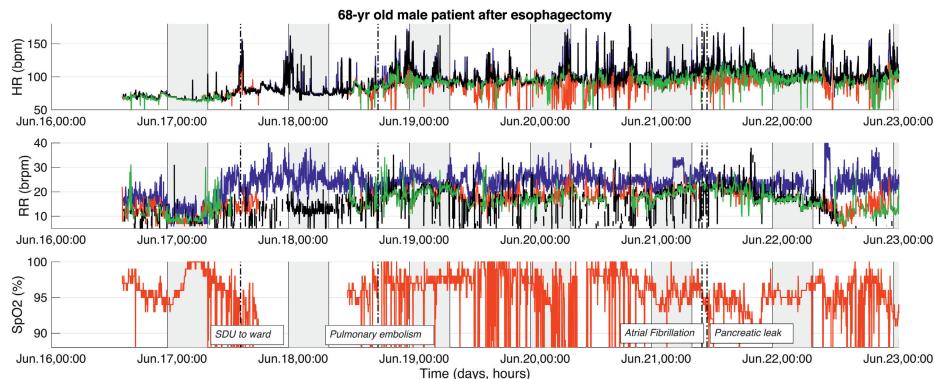

Figure 3. Example of a patient who developed an adverse event, while vital signs were recorded continuously on the surgical ward with the wireless patch sensor (SensiumVitals: black), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas.

Figure 4 shows HR, RR and SpO_2 trends on day 6, 7 and 8 of a 54-year male patient admitted with multiple rib fractures, grade IV liver laceration and a hemopneumothorax after a fall from height. In the morning of May 10th, the chest drain was removed, but after an attempt to reduce oxygen administration oxygen therapy had to be increased. In the afternoon of May 10th, a recurrent pneumothorax was diagnosed, for which conservative treatment with patient-controlled analgesia was initiated. On May 11th, the patient complained of increasing pain, despite adequate pain treatment, after which the patient was readmitted to the SDU with respiratory insufficiency. In the hours before and after this event, HR gradually increased from 70 to 100 bpm. At the same time, RR increased from 16 to 30 brpm. Oxygen saturation frequently decreased below 90%, despite oxygen therapy.

Figure 5 shows the vital sign trends from the 3d to 5th day postoperatively of a 51-year male trauma patient admitted with fractures of the transverse processes of the lumbar vertebrae, sacral fractures and a dislocated femur fracture for which he received pelvic fracture surgery. In the night of May 24th, the patient suddenly developed respiratory insufficiency and was diagnosed with

atelectasis, for which he was readmitted to the SDU. The following changes in vital signs can be seen before this event was diagnosed: the existing tachycardia further increased from 100 to 120 bpm. At the same time, RR increased from 20 to 30 brpm and his oxygen saturation rapidly decreased below 88%.
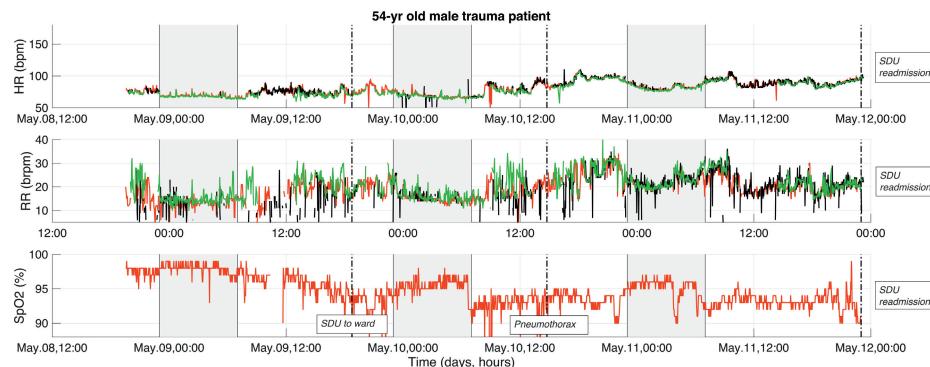
Figure 4. Example of a patient who developed an adverse event, while vital signs were recorded continuously on the surgical ward with the wireless patch sensor (SensiumVitals: black), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas.
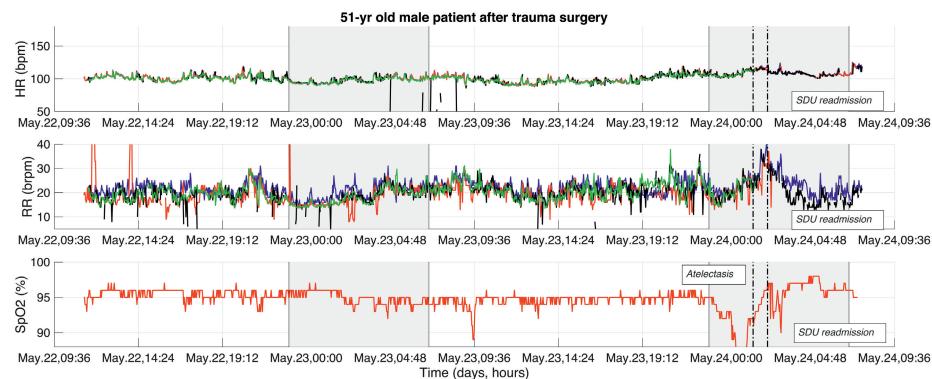

Figure 5. Example of a patient who developed an adverse event, while vital signs were recorded continuously on the surgical ward with the two wireless patch sensors (SensiumVitals: black, HealthPatch MD: blue), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas.
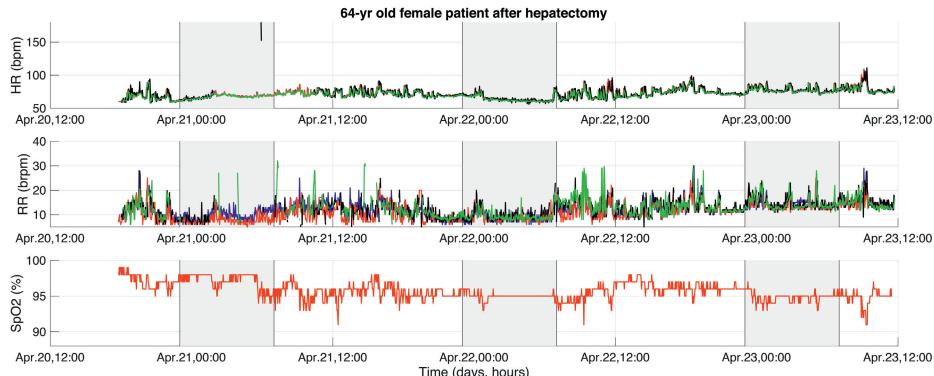
Figure 6. Example of a patient in whom vital signs were recorded continuously on the surgical ward with the two wireless patch sensors (SensiumVitals: black, HealthPatch MD: blue), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas. No adverse events occurred during the measurement period.

4

Descriptive analysis of vital signs recordings of patients without occurrence of adverse events

Figure 6 shows the vital signs of a 64-year old female patient 2 days after hepatectomy surgery without development of adverse events. A short period of tachycardia can be noticed early in the morning on April 23. This corresponds with a brief period of patient mobilization, since no measurements of the bed-based EarlySense system are present. In addition, no sustained tachypnea can be recognized. SpO_2 slowly decreased over time, but remained stable.
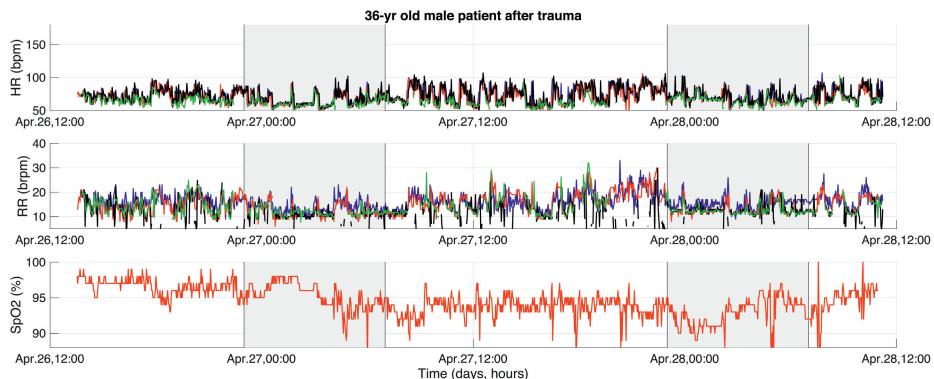
Figure 7. Example of a patient in whom vital signs were recorded continuously on the surgical ward with the two wireless patch sensors (SensiumVitals: black, HealthPatch MD: blue), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas. No adverse events occurred during the measurement period.

Figure 7 shows HR, RR and oxygen saturation of a 36-male patient admitted with multiple rib fractures and a pneumothorax after a motorcycle accident. This patient did not develop complications during hospital stay. Frequent short periods of tachycardia can be seen in Figure 7, which correspond with periods of mobilization. During mobilization, respiration rate increased slightly too, but no sustained periods of tachypnea were observed. In the morning of April 27th, oxygen administration was stopped. During this period, oxygen saturation decreased to 95%, but it remained stable over time.

Figure 8 shows vital sign recordings of a 70-year old male patient admitted with multiple rib fractures and hemothorax after a fall from height. No adverse events occurred during hospital stay. There were no episodes with sustained tachycardia. Respiration rate slowly decreased during the night and slightly increased in the morning during periods of mobilization. Oxygen saturation remained stable around 94-96% over time.
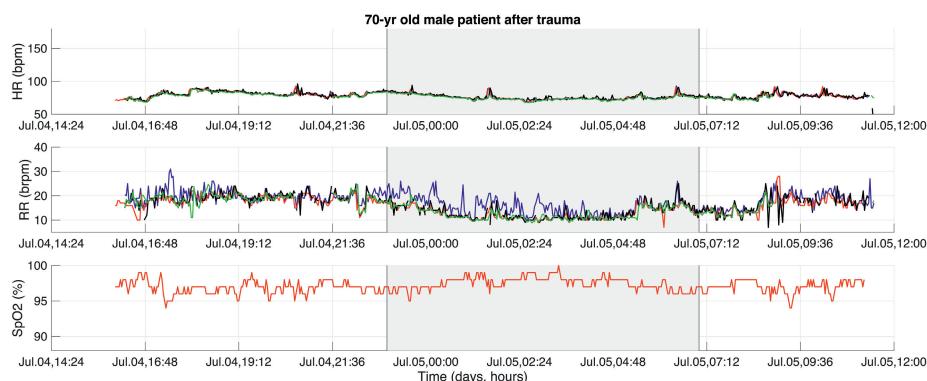
Figure 8. Example of a patient in whom vital signs were recorded continuously on the surgical ward with the two wireless patch sensors (SensiumVitals: black, HealthPatch MD: blue), the bed-based system EarlySense (green) and a patient-worn monitor (Masimo Radius-7: red). The night from 11 p.m. to 7 a.m. is illustrated by shaded gray areas. No adverse events occurred during the measurement period.

Summary of adverse events

An overview of adverse events is summarized in Table 3. All four patients that developed new-onset AF after esophagectomy also developed other postoperative complications, such as an anastomotic leak, pneumonia or pneumothorax. During AF, a sudden increase in HR or gradual increase in HR was recognized in all four vital sign recordings. However, differences exist among sensors to capture AF with rapid ventricular rate. Both Masimo-Radius 7 and EarlySense underestimate the actual heart rate during periods of AF whereas HealthPatch MD and SensiumVitals did not.

Patients that became respiratory insufficient showed an increase in RR and a decrease in SpO2. Most patients showed an increase in HR as well, although this was not always clearly visible. In patients with mild pneumonia, who did not develop respiratory insufficiency, changes in vital signs were often minor or ambiguous.

In vital sign recordings of patients without adverse events, temporary periods of high HR and RR can be observed as well. However, these periods occurred less frequent, were often transient and less severe when compared to patients who subsequently developed an adverse event. In addition, none of the patients without adverse events showed substantial simultaneous changes in HR and RR, except for short episodes during mobilization.

Discussion

The ability of currently available wireless vital signs sensors to detect adverse events in a group of high-risk surgical patients and also vital sign trend patterns in patients who did not develop adverse events during the measurement period were evaluated in this study. The current first generation of wireless sensors were shown to detect abnormalities in vital sign trend patterns before adverse events were diagnosed. In patients without adverse events, periods of tachycardia and tachypnea did occur, but these changes occurred less frequently and were often transient. Furthermore, none of the patients without adverse events showed simultaneous increases in HR, RR and SpO_2, except during periods of mobilization.

During AF, a clear trend in HR was recognized in all recordings. All four patients that developed new-onset AF after esophagectomy also developed other adverse events. It may be as such of predictive value for developing other postoperative complications. This finding is consistent with previous studies that showed a high association between AF and various postoperative infectious complications [17,18].

Interestingly, this study also shows differences among the studied wireless sensors to capture AF with rapid ventricular rate. Masimo Radius-7 underestimates the actual heart rate since it calculates heart rate from the plethysmographic waveform obtained from the pulse oximeter probe. Similarly, the EarlySense system may underestimate the actual heart rate during periods of AF, since it derives HR from cardiac ballistic movement associated with ejection of blood with each heart cycle. During AF with rapid ventricular rate many beats will have had insufficient time for ventricular filling as a result undetectable peripheral pulse. Both patch sensors SensiumVitals and HealthPatch MD derive heart rate form ECG and show therefore higher accuracy for HR during periods of AF [19,20].

The vital sign trends of the patients that became respiratory insufficient showed an increase in RR and a decrease in SpO_2. Most patients showed a simultaneous increase in HR, although this was not always clearly visible. In patients with mild pneumonia who developed no respiratory insufficiency for example, clear changes in vital signs were not always present.

Even during periods of hemodynamic and respiratory stability, decreases in SpO_2 (<90%) are recognized, although less frequent in patients who did not develop adverse events. With the current single parameter 'threshold' based alarms, this

would have resulted in a high number of false-positive alerts which could lead to highly undesirable alarm fatigue among ward nurses [21]. However, if RR, HR and SpO2 patterns deteriorate simultaneously as shown in the present study, a much stronger predictive value for patient deterioration arises.

The present study provides a first glance of the capability of first-generation wireless monitoring systems. The fact that patient deterioration is often preceded by changes in vital signs is not new, but so far no studies have evaluated the ability of one or more wireless systems to detect deteriorating vital sign trend patterns in patients that deteriorate on a general ward. A few studies have demonstrated the potential of continuous vital signs monitoring systems on the ward. In a recent study of postsurgical patients of which blood pressure was continuously monitored with the ViSi Mobile system on the ward, Turan et al. [22] showed that nearly half of the patients experienced severe hypotension (mean arterial pressure < 65mmHg) for more than 15 min which were missed by routine nursing rounds. In another study, the MEWS was calculated every 30 min with two remote monitoring solutions (ViSi mobile system and HealthPatch) and compared to regular MEWS measurements of nurses [23]. Recordings of these remote monitoring systems resulted in periods of high MEWS, most of them during the evening and night, indicating that potentially alarming situations were missed. Although both studies show potential advantages of continuous vital signs monitoring on the ward, these studies did not show to which extent periods of either severe hypotension or high MEWS was associated with patient deterioration. In addition, both studies did not evaluate the value of vital sign trends in predicting clinical deterioration.

A large number of studies have been published on the use of Modified Early Warning Scores (MEWS) to recognize patient deterioration early and initiate therapy, including Rapid Response team activation [12,24-26]. Until now, such studies only used intermittently recorded vital signs when calculating a score. Scores that include trends over time typically use the change since the last vital observation [27,28]. However, no studies are available yet that report on the ability of continuous wireless monitoring solutions to identify patient deterioration early.

This study was designed to validate the sensor accuracy of four different remote monitoring systems, not to clinically monitor surgical patients. As a result, the sample size and number of adverse events was too small to identify specific vital signs patterns for each type of adverse event. Nevertheless, despite a relatively

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low number of adverse events, these results do provide insight in the ability of the current generation of wireless sensors to assist in more timely detection of patient deterioration.

Although most of the adverse events in the present study occurred during ward admission, some of the complications were diagnosed during SDU stay where continuous surveillance monitoring was already in place. However, this study did not focus on the ability to recognize patient deterioration earlier, but to show to what extent current wireless monitoring systems are capable to detect vital sign patterns of patient deterioration.

The potential benefits of wireless patient monitoring on the ward with wearable sensors are increasingly being recognized in literature [23,29-31]. To succeed in developing reliable patient monitoring systems, wireless sensors need to be connected to sophisticated signal analysis and alarm notification systems to inform nursing staff on time, while at the same time minimizing false-positive alerts. Future large studies in high-risk patients are therefore needed to obtain sufficient amount of data to validate algorithms designed to reliably identify patient deterioration.

Conclusions

Current systems for wireless monitoring of patients on the ward are capable of recognizing vital signs abnormalities in surgical patients who develop adverse events. Remote patient monitoring may have potential to generate early warnings for patient deterioration to nursing staff and could as such contribute to improved patient safety. To prevent unacceptably high false-positive alarm rates, future systems might benefit from improvements in the deterioration detection algorithms and alert systems to pave the way for predicting clinical deterioration and early interventions.

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Chapter 5

A proposed test protocol for new wearable wireless vital signs sensors

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Abstract

Background: The promises of wearable and wireless vital signs sensors to capture patient deterioration earlier are enormous, although evidence on reliability and usability often remains unclear or questionable. The current regulatory pathway only requires manufacturers to demonstrate that their device can measure the intended vital signs, e.g., heart rate or blood pressure. There is no requirement to show that sensors accurately measure vital signs across the full range of values encountered in the deteriorating patient. Therefore, clarity is needed regarding requirements and methodologies for validation studies.

Objective: This study aimed to design and apply a test protocol assessing the validity, reliability and usability of new wearable wireless sensors for continuous vital signs monitoring.

Methods: A 90-minute test protocol was designed that mimics typical real-life situations in which vital signs sensors could be employed. We illustrated how the protocol might be used by evaluating the performance of four prototype wearable, wireless, multi-parameters sensors during a method comparison study under 'laboratory' conditions and subsequently during five days of 'field-testing' at home. Outcome measures were 95% limits of agreement and concordance rate. Clarke Error Grid analysis was performed to assess the clinical accuracy. Overall data loss during periods of activity and rest were analyzed. In addition, usability was evaluated with a questionnaire and the System Usability Scale (SUS).

Results: Twenty volunteers (10 in London and 10 in Utrecht, average age: 64 years) executed the test protocol and wore each of sensors at home in a rotating order. Testing of agreement and concordance of heart rate, respiratory rate, non-invasive blood pressure and skin-temperature of the prototype sensors versus reference standards showed considerable variation across devices. High percentages of data loss (>35%) for two devices were seen. The mean SUS score varied from low usability of Device A (mean 53) to 'ok' usability for Device C (mean 67).

Conclusions: the designed 90-min test protocol with 5-day of field-testing is suitable to highlight several strengths and weaknesses of (prototype) wireless wearable sensors for remote vital signs monitoring.

Introduction

Recent advances in sensor and wireless technology have enabled the development of small wearable wireless sensors to continually measure physiological vital signs. These devices have potential to improve patient safety in hospital, and also to facilitate novel care concepts such as 'hospital at home' which may reduce hospital length of stay and prevent the need for hospitalization altogether in some cases.

Unfortunately, the current regulatory pathway to approval of wearable wireless sensors leaves much to be desired [1]. In essence, at present it only needs to be demonstrated that the devices can, usually in artificial conditions, measure the intended vital sign(s), e.g., heart rate. There is no requirement to show that the sensors accurately measure vital signs across the full range of values encountered in chronic disease and acute illness, or to establish that they will genuinely benefit patients in clinical practice. As a result, the market has been flooded with devices with unknown or questionable validity, reliability, or value. However, new European Medical Device Regulation taking effect in May, 2021 requires that safety investigations and clinical validations are performed before certification is granted [2]. It is therefore essential to have clarity regarding the requirements and methodologies for such studies. For example, one imperative is that as patient movement is thought to be the main cause of signal artefacts and invalid vital signs measurements, test protocols should include several different tasks that require participants to perform typical movements, e.g., changing position in bed, getting out of bed, walking or climbing stairs.

The purpose of this work was to design a test protocol that mimics some typical real-life situations in which wearable wireless vital signs sensors could be employed, and to illustrate how the protocol might be used with examples of test processes undertaken by the authors. It was prompted by the need to select the most promising designs for such sensor systems within the competitive *Nightingale H2020* pre-commercial procurement project (www.nightingale-h2020.eu). This is an EU-funded initiative with five European academic hospitals (Utrecht, the Netherlands; Stockholm, Sweden; London, United Kingdom; Leuven, Belgium and Aachen, Germany) stimulating industry to develop the next generation of wearable wireless vital signs sensors and analytic software. The software component is needed to produce intelligent alerts signaling only when there is a high probability of clinical deterioration

rather than using simple the threshold-based systems generating numerous false positives mostly used at present [3,4]. Discussion of the validation of clinical decision support software is beyond the scope of the current paper, which is solely concerned with sensor validation processes. The aim of this study was to design and apply a test protocol to assess the validity, reliability and usability of new wearable wireless sensors for continuous vital signs monitoring.

Methods

Any study using medical devices in humans (volunteers or patients) must conform to ethical principles laid out in the Helsinki declaration [5] and be approved both by the local ethical review board and the appropriate national regulatory body tasked with overseeing the validation and introduction of new medical devices. For the present study, we obtained ethical committee approval in London and Utrecht as well as regulatory approval from the *Medicines & Healthcare products Regulatory Agency* in the UK, and the *Dutch Inspectorate for Health and Youth* in the Netherlands.

Selection of study participants
We followed the advice of the patient representative of the expert panel that monitors the progress of EU-funded projects who recommended recruitment of 'former patients' rather than young volunteers; as former patients will have experience with one or more previous hospitalizations and should be more able to balance potential value with usability issues of sensor technology as compared to volunteers without any hospitalization experience. It is tempting to perform such studies with healthy young volunteers – because they are relatively easy to recruit - but this approach is less likely to identify problems with obtaining high quality signals from the type of patients most frequently admitted to hospital; such as elderly or obese individuals. In reference to this, in the multi-national prospective observational cohort METHOD studies of high-risk hospital patients, the mean age was 68 ± 8.2 years; and 40% were assessed as frail [6,7]. We recruited twenty volunteers in London and Utrecht, made sure that at least half were 65 years of age or older and that 30% of volunteers had a Body Mass Index of at least 30 kg/m^2. Exclusion criteria in our project were individuals with known allergy/skin irritation to the adhesives used in standard ECG electrodes, presence of implanted medical devices such as cardioverter / defibrillators or pacemakers, or current pregnancy. Having obtained written consent was obtained from the

volunteers, use of the test protocol started with application of one of the four prototype sensor systems described in detail below.

Description of four prototype wireless sensors

We investigated the performance of four early prototypes of wearable wireless multi-parameter sensors developed by four competing manufacturers. Two devices were lightweight multi-parameter sensors attached to the chest with standard electrocardiogram (ECG) electrodes. A third device was placed on the upper arm and the last device was held in place on the chest with a flexible chest strap. The latter two devices did not use ECG electrodes. One sensor was designed as a single-use disposable unit, whereas three were rechargeable and reusable. Various measurement techniques were involved - and often combined - in the sensor designs, such as ECG, ballistocardiography, phonocardiography, impedance pneumography or photoplethysmography (PPG). All four devices were able to measure heart rate, respiratory rate, skin temperature and motion. Two of the prototype devices had working early versions of software to determine continuous noninvasive blood pressure (NIBP) and oxygen saturation (SpO$_2$); but these functions are not reported here, noting that the test protocol does not involve a hypoxic challenge.

Testing performance of novel wearable wireless vital signs sensors

A complete wearable wireless sensor validation protocol consists of four phases:

1. Mandatory electrical safety and bench tests (performed by medical engineers of the hospital medical physics department)
2. An initial 'methods comparison' study in volunteers, where for every vital sign parameter, the agreement between the prototype sensor's values and a commercial hospital-grade multi-parameter patient monitor is compared. Here we tested respiratory rate, heart rate, skin temperature, as well as the cuff-less NIBP on the two devices with those functions.
3. Usability tests in volunteers, with a period of '*field testing*' (e.g., five days) where participants wear the sensor systems day and night at home to assess the quality of data transmission and to obtain information on usability from the patient perspective.

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For prototypes in the final development phase that have successfully passed the tests in phases 1-3, a final phase to determine real-life clinical performance needs to be executed:

4. A clinical validation study with hospitalized patients attached to established multiparameter monitors, e.g., in the intensive care unit, operating theatre, the recovery room following surgery or if monitored continuously in a step-down unit [8,9]. This final phase is necessary to ensure that the sensor performance is also assessed in the abnormal, pathophysiological range of vital signs. It is important to select patients at high risk of deterioration, to make sure that at least several 'deterioration events' will be encountered. (This validation phase has not yet taken place in our project and will be the subject of a future paper.)

Study design and setting

In our study, all twenty volunteer participants wore each of the four prototype sensors each in turn during the methods comparison period (phase 2) and then in field testing (phase 3), with the devices worn in a counterbalanced schedule so that participants experienced the devices in a rotating order. We gave break of at least two full days between each period of five days field testing.

Methods comparison study (Phase 2)

The methods comparison phase in our project was conducted under 'laboratory conditions' in quiet rooms, using commercial hospital-grade critical care multi-parameter vital signs monitors as clinical reference standards; a GE Dash 4000 (GE, Boston, MA, United States) in London and Spacelabs *XPrezzon* (Spacelabs, Snoqualmie, WA, United States) in Utrecht. Both reference monitors utilize thoracic bioimpedance changes from the ECG electrodes to derive respiratory rate, a technique known to be very sensitive to motion artefact. Therefore, we also employed acoustic respiratory rate measurements as the reference for respiratory rate, using an adhesive patch on the neck (RRa, Masimo Corporation, Irvine, CA, United States). This acoustic sensor detects tracheal breath sounds and derives respiratory rate by signal processing of the audio waveform. Acoustic respiration rate measurement has been shown to correlate well with capnography in several validation studies [10,11]. An overview of the reference standards is shown in Supplementary File 1.

Every volunteer was asked to execute a test protocol that included periods of rest and activity, such as walking, lying in bed or deep knee flexions (Table 1). As part

of this test protocol, we asked volunteers to breathe at different rates guided by a visual metronome at various points in the sequence in order to test the sensors performance at relatively low (6/min), normal (12/min) and high (24/min) respiratory rates. The entire sequence was typically completed in 85-90 minutes, but an option of adding one or more brief rest periods should be allowed for, as might be needed by an elderly or frail person. The complete test protocol we developed with each of the successive steps is shown in Table 1.

Usability testing (field testing; Phase 3)

During our field testing, volunteer participants wore each device continuously for a five day period and reported in a diary their main activities of daily living, as well as generic and specific aspects of usability such as ease of use, skin irritation or wearing comfort. At the end of the field test, each volunteer reported their overall assessment of usability of each device with the validated System Usability Scale (SUS) [12] questionnaire and also aspects of comfort and ease of use on a 5-point Likert scale (Supplementary File 2).

Signal analysis

The raw data transmitted by each of the prototype sensors and reference systems in our study were retrieved in comma-separated values or text file format. Data were stored and processed using Matlab (The MathWorks, Natick, MA, USA). Non-physiological outliers (for example, a respiratory rate > 45) were removed from both the reference monitors and prototype sensors. For heart rate, NIBP and skin temperature, the routine hospital monitoring systems were used as reference standard. For respiratory rate comparison, the acoustic RRa patient-worn monitor was used as reference standard. Sensor data and reference data were synchronized based on cross-correlation to ensure alignment of their respective time stamps. Data reports from the reference monitor contained vital signs data sampled once per minute (both hospital multiparameter monitoring systems) or every 2 seconds (RRa, Masimo). NIPB was measured every 5 min. The update rate of all four prototype sensors varied from once every second to once every minute. For heart rate, respiratory rate and skin temperature, the prototype sensor data was averaged to once per minute (i.e., a median over 60 s was taken) to produce paired data points with the reference standard. For NIBP, a median over the previous 60 s was calculated and compared to the nearest time point of the reference monitor.

Outcomes and Statistical analysis

We used Bland and Altman analysis for repeated measurements to assess the agreement between vital signs captured by the prototype devices and by the reference monitors during periods of activity and rest [13]. Our testing showed that the pre-defined acceptable limits of prototype sensor agreement with the established systems, which we had decided and shared in advance with our four manufacturers were in fact too strict. Those limits were based on specifications described in bench tests of critical care monitors which do not take into account real-world issues of monitoring patients or volunteer participants in periods of reduced reliability, e.g., during movement or talking. Consequently, a concordance rate analysis was performed. The concordance rate, which is defined as the ratio (percentage) of a vital sign assessed by the prototype sensor and the established reference that both change in the same direction (decreasing or increasing) was calculated for each vital sign, except skin temperature [14] . We used an exclusion zone of 1 beat/min for heart rate, 1 breath/min for respiratory rate and 1mmHg for NIBP. Determining the accuracy of oxygen saturation was beyond the scope of testing in volunteers at this early stage, since no decreased oxygen levels in volunteers are expected.

In addition, a Clarke Error Grid analysis was conducted to quantify clinical accuracy of the prototype sensors against the reference standard and to study the potential consequences for treatment decisions [15]. Another objective of the test protocol was to assess the data continuity during execution of the test protocol. This was tested since all devices required a Bluetooth connection to a gateway device that uploads the data over cellular networks to a cloud server. Data continuity was defined as the overall amount of data loss during periods of activity and rest.

Table 1. Outline of a test sequence for the initial methods comparison study of new wearable wireless vital signs sensors in volunteer participants

Block (Type)	Task	Description	Duration (minutes)	Cumulative (minutes)
Rest	Sitting (chair next to bed)	The participant is seated in a chair next to bed. He or she can cross one leg over the other.	10	10
Active	Call someone using mobile phone	While seated in the chair, the participant is asked to call someone (e.g., the researcher) and talk for 2 minutes	2	12
Rest	Lying (supine)	The participant moves from the chair into bed and is asked to lie down on their back. *Lying on back with head on a pillow.*	4	16
Metronome	Visually-guided metronome breathing (sitting in chair next to bed)	Metronome breathing 6 breaths/min *Visual cue each 10 sec*	3	19
Metronome	Visually-guided metronome breathing (sitting in chair)	Metronome breathing 15 breaths/min *Visual cue each 4 sec*	3	22
Metronome	Visually-guided metronome breathing (sitting in chair)	Metronome breathing 20 breaths/min *Visual cue each 3 sec*	3	25
Metronome	Visually-guided metronome breathing (sitting in chair)	Metronome breathing 24 breaths/min *Visual cue each 2.5 sec*	3	28
Rest	Sitting (chair next to bed)	Six minutes of rest after metronome breathing. The participant stays seated in a chair next to bed.	6	34
Active	Basic step	Basic step (staircase walking, use a step)	2	36
Active	Standing upright	Standing (at a standing desk)	6	42
Rest	Lying (supine)	The participant moves into bed and is asked to lie down on their back.	2	44
Rest	Lying (side)	The participant is asked to lie down on either left or right side with head on a pillow.	5	49
Rest	Lying (prone)	Lying on stomach with head on a pillow.	5	54
Active	Walking (slow)	Step out of bed. Walking around bed at slow speed.	6	60

Table 1. Continued.

Block (Type)	Task	Description	Duration (minutes)	Cumulative (minutes)
Rest	Leaning backwards	Move to bed again. Seated in a reclining position, with the backrest approximately 45 degrees to the bed. Legs could be straight, or knees bent with feet on bed. Possibility to read	10	70
Active	Deep knee flexions	Move out of bed. Deep knee flexions	2	72
Active	Lace your shoes	Lace your shoes (or attempt to) and move around	2	74
Rest	Sitting (chair next to bed)	The participant is asked to move to take a seat in the chair.	10	84
Rest: Active: Metronome: *In total*			52 minutes 20 minutes 12 minutes *84 minutes*	

Test Results

All four prototype wearable wireless sensors in our project passed mandatory electrical safety tests in both hospitals (phase 1). From April to October 2019, a total of 21 volunteers entered the study, of whom 19 performed both the test protocol (phase 2) and field-testing at home (phase 3). Two volunteers either performed phase 2 or 3. The average age of the volunteers was 64 years (range: 22–93) and nine volunteers were 65 years or older. Average BMI was 26 (range: 18-51) kg/m^2, with 6 having a BMI > 30 kg/m^2. Seven volunteers were living alone.

Results of the methods comparison validation

Testing of agreement and concordance of the prototype wearable wireless vital signs sensors versus reference standards showed considerable variation across devices, across different vital signs, and at times of rest and activity as can be seen in Table 2. Device A and B had high concordance for heart rate measurements both during periods of rest and activity, whereas Device C and D showed low concordance rates during both periods. Clarke Error Grid analyses of heart rate during periods of rest (Figure 1A-D) and activity (Figure 2A-D) confirmed these differences in clinical accuracy. Device D overestimated heart rate at rest. It also showed a high percentage of measurements in region C or D, which means that these measurements could lead to unnecessary treatment or potentially dangerous failure to detect tachycardia. Device C underestimated increasing heart rate levels during periods of activity. For respiratory rate, the concordance rate of Device A, Device B and Device C with the reference standard was acceptable, whereas Device D showed a low concordance rate during rest and activity periods. Clarke Error Grid analyses of respiratory rate during rest of Device D (Figure 3A-D) and during activity (Figure 4A-D) showed relatively high numbers of respiratory rate measurements in region B, which means that these measurements are outside 20% of the reference standard, although this might not lead to unnecessary treatment. Blood pressure accuracy could only be evaluated for devices B and C; the other two devices had no testable blood pressure algorithms yet. Comparison of systolic blood pressure measurements with the reference standard showed low concordance and

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Table 2. Bland-Altman Analysis and Concordance Rate analysis for heart rate, respiratory rate, systolic blood pressure and skin temperature from the wireless sensor prototypes versus reference standards

Vital sign	Periods of Rest							Periods of Activity						
	Volunteers (n)	Measurement pairs (N)	Bias	Lower 95% LoA	Upper 95% LoA	Concordance Rate (%)		Volunteers (n)	Measurement pairs (N)	Bias	Lower 95% LoA	Upper 95% LoA	Concordance Rate (%)
Heart Rate														
Device A	20	1209	0,4	-9,2	10,1	90		20	334	-0,7	-15,8	14,4	94
Device B	20	1103	1,2	-13,9	16,3	82		20	308	-1	-19,4	17,3	81
Device C	20	535	-2,7	-17,5	12,1	48		16	102	-17,3	-48,5	13,8	61
Device D	20	1032	18,0	-47	83	54		20	271	4,5	-69,2	78,1	48
Respiratory Rate														
Device A	20	1014	-1,5	-8,3	5,3	87		20	276	-0,7	-8,7	7,4	74
Device B	20	974	-1,8	-11	7,2	73		20	322	-1,1	-11,2	9,1	71
Device C	20	811	0,9	-6	7,8	78		19	192	1,2	-6,8	9,3	76
Device D	20	909	1,1	-9,4	11,6	61		20	221	1,4	-8,4	11,3	61
Systolic Blood Pressure														
Device B	20	178	6,9	-29,5	43,3	53		20	40	0,2	-46,4	46,7	50
Device D	20	211	0,4	-28,3	29	63		20	38	-6,6	-45,1	32	20
Skin Temperature														
Device A	19	974	4,6	1,2	8,1	NA		19	270	5,5	2,5	8,5	NA
Device B	15	856	0,8	-3,2	4,9	NA		15	243	1,5	-2,6	5,6	NA
Device C	20	1031	0,2	-4,2	4,5	NA		18	260	0,5	-2,8	3,8	NA
Device D	18	871	2,8	-0,2	5,9	NA		18	186	3,4	-0,9	7,8	NA

wide limits of agreement for both Device B and D during periods of rest and activity (Table 2). All four devices showed wide limits of agreement for skin temperature measurements. Device A and Device D overestimated skin temperature with a mean difference of 4.6 °C or 2.8 °C during rest respectively and 5.5 °C or 3.4 °C during periods of activity.

An overview of overall data loss of each prototype sensor during execution of the test protocol in our project is shown in Table 3. Device C showed very high percentages of data loss for both heart rate (50.6% during rest, 60.2% during activity) and respiratory rate (23.8% in rest, 35.3% during activity) measurements, an issue that was later found to be caused by Bluetooth communication programming issues. From Device D, more than half of the respiratory rate data was not available during rest (56.4%) whereas 28.4% of the data was missing during periods of activity.

Results of field testing

Volunteer participants' evaluation of the usability of the wearable wireless sensor systems when worn at home over a continuous five-day period is summarized in Table 4. The results show that usability of Device A was low (mean SUS score: 53) and usability was 'ok' for Device B (mean SUS score: 67), Device C (mean SUS score: 66) and Device D (mean SUS score: 65). The wearability of the prototype sensors varied. 55% of the participants reported high comfort wearing of Device C or D; they were not aware or only sometimes aware of wearing the sensors, whereas 40% of the participants were continuously or usually aware of wearing Device A or B (Table 4). Furthermore, devices that required disposable ECG electrodes (Devices A and B) were not acceptable to all volunteers, as some developed a skin rash or irritation (itching) after wearing these for more than a day.

Table 3. Overall data loss of each prototype sensor during in-hospital tests

Percentage of Total Data Loss		
Vital sign	During Rest	During active periods
Heart Rate		
Device A	6,6	8,1
Device B	11,1	8,8
Device C	50,6	60,2
Device D	15,1	9,2
Respiratory Rate		
Device A	6,5	18,5
Device B	3,4	4,4
Device C	23,8	35,3
Device D	56,4	28,4
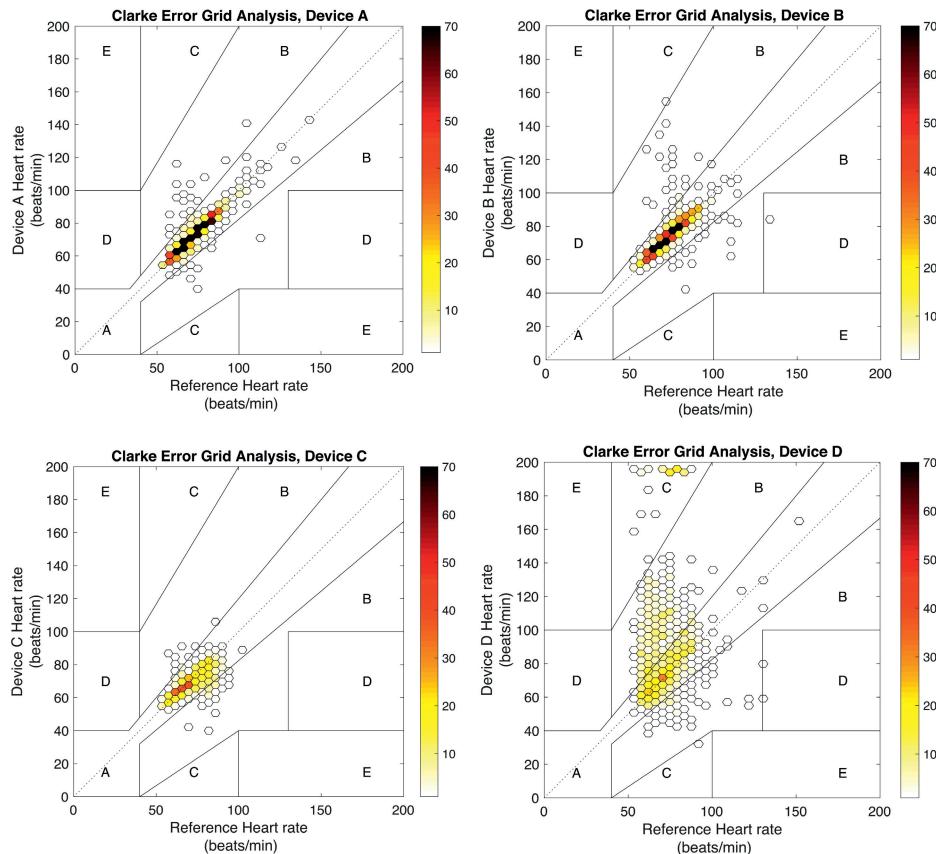
Figure 1A-D. Clarke Error Grid analysis to quantify clinical accuracy of the heart rate measurements during periods of rest with Device A, Device B, Device C and Device D as compared with the reference standard. The colored dots are measurement pairs each superimposed on the Error Grid boundaries, where the color intensity is proportional to the number of observations. Region A encloses points within 20% of the reference monitor; region B contains points outside 20% of the reference, but not leading to unnecessary treatment. Region C contains points leading to unnecessary treatment, region D indicates a potentially dangerous failure to detect bradycardia or tachycardia, and region E represents points where events are confused (e.g., bradycardia with tachycardia).

Figure 2A-D. Clarke Error Grid analysis to quantify clinical accuracy of the heart rate measurements during periods of activity with Device A, Device B, Device C and Device D as compared with the reference standard. The colored dots are measurement pairs each superimposed on the Error Grid boundaries, where the color intensity is proportional to the number of observations. Region A encloses points within 20% of the reference monitor; region B contains points outside 20% of the reference, but not leading to unnecessary treatment. Region C contains points leading to unnecessary treatment, region D indicates a potentially dangerous failure to detect bradycardia or tachycardia, and region E represents points where events are confused (e.g., bradycardia with tachycardia).

Figure 3A-D. Clarke Error Grid analysis to quantify clinical accuracy of the respiratory rate measurements during periods of rest with Device A, Device B, Device C and Device D as compared with the reference standard. The colored dots are measurement pairs each superimposed on the Error Grid boundaries, where the color intensity is proportional to the number of observations. Region A encloses points within 20% of the reference monitor; region B contains points outside 20% of the reference, but not leading to unnecessary treatment. Region C contains points leading to unnecessary treatment, region D indicates a potentially dangerous failure to detect bradypnoea or tachypnoea, and region E represents points where events are confused (e.g., bradypnoea with tachypnoea).

Figure 4A-D. Clarke Error Grid analysis to quantify clinical accuracy of the respiratory rate measurements during periods of activity with Device A, Device B, Device C and Device D as compared with the reference standard. The colored dots are measurement pairs each superimposed on the Error Grid boundaries, where the color intensity is proportional to the number of observations. Region A encloses points within 20% of the reference monitor; region B contains points outside 20% of the reference, but not leading to unnecessary treatment. Region C contains points leading to unnecessary treatment, region D indicates a potentially dangerous failure to detect bradypnoea or tachypnoea, and region E represents points where events are confused (e.g., bradypnoea with tachypnoea).

Overall, our volunteer participants particularly valued simplicity in the prototypes, preferring the more unobtrusive devices that could be forgotten about. Some of the procedures regarding changing of sensor devices after recharging the battery turned out to be too complex, particularly for older participants. Interestingly, individuals tended to blame themselves, rather than the design of the device. For example, one volunteer aged 93, was unable to reattach a recharged device to the ECG electrodes, because they were obscured by the device (Device A; Table 4). He commented: "I am very sorry doctor, but I am too old and too stupid for

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this device". Another challenge was the device that had a 'on/off' micro-switch that could only be switched using a pen.

As all devices required both successful Bluetooth pairing as well as sufficient cellular connectivity to transfer the data from the relay smartphone or dedicated gateway device to a server, we uncovered several vulnerabilities. For example, one vendor provided SIM cards that did not work reliably with the telecom operators in the Netherlands and as a result, very little data was transferred to the server during the field tests at home.

Few individuals were particularly interested in having a view of their vital signs data, which they were able to see on the dedicated smartphone relay component of Device A, B and D. Some volunteers even reported that it made them nervous that they were able "to see every data point". In addition, Device B showed additional technical status messages, such as 'no connection to server'. Such messages were perceived as worrisome by a few volunteers, as they were not actionable. Device C did not have the functionality to show any vital signs data or other information on their relay.

Table 4. Scores of each of the usability categories and the System Usability Scale

Category	Response	Device A	Device B	Device C	Device D
		n (%)	n (%)	n (%)	n (%)
Aware of wearing sensor	Continuously	2 (10)	4 (20)	0 (0)	1 (5)
	Usually aware	6 (30)	4 (20)	4 (20)	3 (15)
	Somewhat aware	4 (20)	6 (30)	5 (25)	5 (25)
	Only sometimes aware	7 (35)	6 (30)	8 (40)	11 (55)
	Not aware	1 (5)	0 (0)	3 (15)	0 (0)
Extent of irritation skin	Always irritating	1 (5)	0 (0)	0 (0)	0 (0)
	Frequently irritating	4 (20)	2 (10)	1 (5)	3 (15)
	Not irritating at first, but after a while	7 (35)	7 (35)	6 (30)	5 (25)
	Not really irritating	5 (25)	7 (35)	3 (15)	5 (25)
	Does not irritate	3 (15)	4 (20)	8 (40)	7 (35)
Extent of interference sleep	Always interfering	0 (0)	0 (0)	0 (0)	0 (0)
	Frequently interfering	1 (5)	1 (5)	1 (5)	0 (0)
	Sometimes interfering	3 (15)	4 (20)	4 (20)	5 (25)
	Not really interfering	10 (50)	8 (40)	3 (15)	8 (40)
	Not interfering	6 (30)	7 (35)	12 (60)	7 (35)

Table 4. Continued.

Category	Response	Device A	Device B	Device C	Device D
Stays in place in case of sweating	Always loosens	1 (5)	1 (5)	0 (0)	0 (0)
	Frequently loosens	2 (10)	2 (10)	1 (5)	1 (5)
	Sometimes loosens	5 (25)	5 (25)	4 (20)	3 (15)
	Stays in place	8 (40)	9 (45)	11 (55)	12 (60)
	Hardly loosens	4 (20)	3 (15)	4 (20)	4 (20)
Easy to change/ charge batteries	Hard and cumbersome	0 (0)	0 (0)	1 (5)	0 (0)
	Hard to change	3 (15)	1 (5)	3 (15)	2 (10)
	Took some time, but was acceptable	9 (45)	0 (0)	6 (30)	0 (0)
	Really easy to change batteries	7 (35)	19 (95)	9 (45)	6 (30)
	No battery change needed	1 (5)	0 (0)	1 (5)	12 (60)
Overall user-friendliness	Very difficult to use	1 (5)	0 (0)	0 (0)	0 (0)
	Difficult to use	4 (20)	2 (10)	2 (10)	2 (10)
	Neither easy to use, nor hard to use	10 (50)	2 (10)	2 (10)	5 (25)
	Easy to use	4 (20)	9 (45)	7 (35)	8 (40)
	Very easy in use	1 (5)	7 (35)	9 (45)	5 (25)
System Usability Scale score		mean (SD)	mean (SD)	mean (SD)	mean (SD)
		53 (15)	67 (13)	66 (20)	65 (16)

Discussion

We designed and applied a test protocol to assess the validity and reliability of novel wearable wireless sensors designed to continuously capture vital signs. The 90 minute methods comparison sessions were well tolerated, even by the oldest participant. Evaluations revealed several strengths as well as some weaknesses in each sensor that would need to be addressed before testing with real patients takes place.

Heart rates were reliable in sensors that obtained an ECG signal from standard ECG electrodes, but were prone to error when obtained from pulse plethysmography on the upper arm or ballistocardiography from the chest, particularly during movement. Respiratory rates at rest derived from impedance pneumography or ballistocardiography were more reliable than readings from PPG. However, frequent data loss of respiration measurements occurred during periods of activity in three of the four devices that use ballistocardiography, PPG or impedance pneumography to capture respiratory rate. These observations suggest that respiratory rate measurements during patient movement should be interpreted with caution. Manufacturers may consider using information from motion sensors to add to abnormal values from PPG, ballistocardiography and impedance pneumography to flag that these might be errors.

Two devices overestimated skin temperature by more than two degrees, possibly because these sensors were 'contaminated' with device-generated heat. Moreover, it is not clear what utility skin temperature could have in early detection of fever or an infection, particularly since changes in skin temperature measurements are sensitive to changes in ambient temperature. Therefore, at present, skin temperature measurements from wearable wireless sensors do not seem to be a reliable proxy for body temperature in patients.

Continuous NIBP readings of two devices were evaluated with the test protocol of the present study. It should be noted, however, that there was only a limited range of blood pressures observed during our tests; i.e., there was no hypotension in any of the volunteer participants at any time and the blood pressure increases during light exercise were modest. In addition, continuous NIBP measurements were compared with 'spot-check' measurements of the reference monitor once every 5 minutes. It should be highlighted that to perform a critical validation study of continuous blood pressure monitoring, patients

with episodes of hypo- or hypertension are needed to determine the reliability of any non-invasive methods used by wireless sensors. Consequently, tests of the accuracy of blood pressure monitoring need to be performed in clinical settings where there are anticipated blood pressure changes, e.g., in the Intensive Care Unit or perioperative setting, and preferably compared to blood pressure measurements from an intra-arterial catheter. Similarly, proper validation of arterial blood oxygen saturation measurements can only be done if hypoxemic levels are included (e.g., SpO_2 values below 90%). This was not possible in our study with healthy volunteers. Rather, testing at altitude or using a high-altitude simulator to generate hypoxic gas mixtures would need to be included in future test protocols.

During the execution of this study we came to realize that published accuracy specifications from bench tests of critical care monitors were obtained under 'ideal' conditions (possibly using only physiological signal simulators) and do not represent real-life clinical performance, particularly the effects of patient movement on signal quality. In Bland-Altman analyses of physiological monitors, the tacit assumption is that the reference monitor is a true 'gold standard' [13,16]. However, we observed that ECG heart rate and respiratory rate obtained from impedance pneumography with the reference ICU monitors were frequently highly inaccurate during motion. One possible explanation is disturbance of the ECG signal from pull on the electrodes during movement that distorts both the ECG signal and respiratory waveform. In clinical practice, ICU nurses looking at the bedside monitor 'filter' these artefacts when interpreting a patient's condition, notwithstanding that more than 85% of alarms are false in the ICU [3,17]. It is therefore unreasonable to expect similar strict limits of agreement from these wireless wearable vital signs sensors as were obtained in bench tests. Indeed, we suggest that some wireless sensors may well be able to outperform traditional 'wired' reference devices in clinical practice. We therefore also performed additional analyses of concordance rate to assess the devices' ability to capture changing vital sign trends.

Ultimately, healthcare needs accurate and reliable user-friendly sensor systems that are acceptable to the many diverse patient groups as well as healthcare staff. Only then will we be able to realize the benefits of continuous remote vital signs monitoring, both in hospitals and at home. Using advanced prediction models to detect patient deterioration and adding options for two-way communication and patient or carer inputs will further facilitate early recognition of patient deterioration, as envisioned in the European Nightingale H2020 project (www-

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nightingale-h2020.eu). However, designing and building the ideal wireless wearable multi-parameter sensor remains a difficult challenge, as seen in the present results.

In conclusion, the test protocol proposed in this study is capable of highlighting the strengths and weaknesses of (prototype) wireless wearable sensors for remote vital signs monitoring. We suggest that sensors intended for continuous vital signs trend monitoring outside high-care facilities need to be critically validated regarding their measurement performance before application in clinical practice. In addition, usability aspects need to be thoroughly tested - and improved where necessary. This is also needed to avoid situations in which patients and doctors – frustrated with excessive false alarm rates and/or usability problems - decide to stop using the sensor system altogether. Nonetheless, considerable progress has been made and there is intense ongoing research and development activity in this important, potentially life-saving domain, suggesting that reliable systems for wireless wearable remote patient monitoring will soon become commercially available.

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Supplementary File 1:

overview of reference standards used during the initial methods comparions validation assessments (Phase 2)

Parameter	Reference standard used at UMC Utrecht, the Netherlands	Reference standard used at UCLH NHS Foundation Trust, UK
Heart Rate	ECG (XPREZZON, Spacelabs Healthcare, Snoqualmie, Washington DC, USA)	ECG (GE Dash 4000 Monitor, General Electric, Boston, MA, USA)
Respiratory Rate	Acoustic monitoring (Radius-7®, Masimo Corporation, CA, USA) Thoracic bioimpedance (XPREZZON, Spacelabs Healthcare, Snoqualmie, Washington DC, USA)	Acoustic monitoring (Radius-7®, Masimo Corporation, CA, USA) Thoracic bioimpedance (GE Dash 4000 Monitor, General Electric, Boston, MA, USA)
Temperature (skin temperature)	Skin Temperature Probe (DeRoyal Industries Inc, Powell, TN, USA)	DermaTemp infrared thermometer (Exergen Corporation WaterTown, MA, USA)
Blood pressure (NIBP)	Non-invasive blood pressure cuff (XPREZZON, Spacelabs Healthcare, Snoqualmie, Washington DC, USA)	Non-invasive blood pressure cuff (GE Dash 4000 Monitor, General Electric, Boston, MA, USA)
Blood oxygen (SpO$_2$)	Pulse oximetry finger probe (XPREZZON, Spacelabs Healthcare, Snoqualmie, Washington DC, USA)	Pulse oximetry finger probe (GE Dash 4000 Monitor, General Electric, Boston, MA, USA)

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Supplementary File 2:

Usability questionnaire to appraise volunteer participants' generic views of each new wearable wireless sensor worn during field testing

Participants are asked to score below 10 items with one of five responses that range from strongly agree to strongly disagree:

1. I think that I would like to use this sensor solution frequently if I need this monitoring.
2. I found the sensor solution unnecessarily complex.
3. I thought the sensor solution was easy to use.
4. I think that I would need the support of a technical person to be able to use this sensor solution.
5. I found the various functions in this sensor solution were well integrated.
6. I thought there was too much inconsistency in this sensor solution.
7. I would imagine that most people would learn to use this sensor solution very quickly.
8. I found the sensor solution very cumbersome to use.
9. I felt very confident using the sensor solution.
10. I needed to learn a lot of things before I could get going with this sensor solution.

The following questions are measured on a 5-point Likert scale:
1. To which extent are you aware of wearing the sensor on your body?
2. I'm continuously aware of its presence. This was very unpleasant
3. I'm usually aware of it's presence.
4. I'm somewhat aware of it's presence.
5. I'm only sometimes aware of it's presence, but this was not unconvenient
6. I'm not aware of it's presence.

To which extent does this sensor irritates the skin?
1. This device was almost always irritating my skin
2. This device was frequently irritating my skin
3. This device did not irritate in the first days, but after a while it was irritating my skin
4. This device was not really irritating my skin
5. This device did not irritate my skin

To which extent does the device interfere with your daily sleep?

1. This device was almost always interfering with my sleep

2. This device was frequently interfering with my sleep

3. This device was sometimes interfering with my sleep

4. This device was not really interfering with my sleep

5. This device did not interfere with my sleep

To which extent does the device stay correctly in place in case of sweating?

1. This device almost always loosens when I start to sweat

2. This device frequently loosens when I'm sweating

3. This device sometimes loosens when I'm sweating

4. This device is not really shower proof, but stays correctly in place when I'm sweating

5. This device hardly loosens, even during a daily shower

To which extent are batteries easy to change? *Note: if no change of battery is needed during these five days, we will ask participants to try this.*

1. It is really hard and cumbersome to change batteries

2. It is hard to change batteries

3. It took some time to change batteries, but this was acceptable to me

4. It is really easy to change batteries. It does not cost a lot of time

5. No battery change was needed

Overall, I would rate the user-friendliness of this product as:

1. Very difficult to use. It requires a thorough training and I needed help with this

2. Difficult to use. It took too much time to learn how to use it.

3. Neither easy nor hard to use. It took some time to learn it, but I accomplished

4. Easy to use and clear.

5. Very easy in use. Everyone can learn this.

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PART 2

Patient deterioration at home after hospital discharge

Chapter 6

Thirty days of home blood pressure monitoring in patients following carotid endarterectomy: a feasibility study

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Abstract

Background and purpose: Hemodynamic disturbances are the causative mechanism in half the perioperative strokes following carotid endarterectomy (CEA). Nevertheless, insight into individual hemodynamics after discharge is lacking. We assessed the feasibility of daily post-discharge blood pressure (BP) self-measurements at home following CEA and analysed BP-trend patterns as well as patient experiences.

Methods: Thirty CEA-patients (age 68±8 years; 87% male) measured BP at home twice daily for 30 days with an ambulatory BP-monitor. Exclusion criteria: Modified Rankin Scale score>2 or no access to WiFi. BP-values were transmitted to an online dashboard on a web application. If individually determined systolic target BP exceeded by ≥15% an alert was generated, and patients were requested to visit the outpatient clinic after 4 consecutive alerts. After 30 days, patients completed a survey regarding their experiences and perceived feasibility of home BP-monitoring. Adherence to the monitoring protocol, BP time-series, and any interventions were scored.

Results: Post-discharge, four adverse events occurred; bleeding requiring surgery (1), TIA (1), myocardial infarction (1), readmission due to stress-related hypertension (1). None of the patients had four consecutive BP-measurements exceeding the BP threshold. Patient adherence was high; 24 patients provided ≥90% of the expected BP-measurements. Eight patients visited their general practitioner with concerns regarding their observed BP-values, in two leading to changes in anti-hypertensive therapy. Over 90% of patients experienced home BP-monitoring as positive and all except one recommended adding home BP-monitoring to standard care. Median intra-individual variability of systolic and diastolic BP of all patients was 12.7 mmHg and 7.4 mmHg, respectively. No significant differences in systolic BP variability or absolute values were found between patients with a post-discharge event and those without.

Conclusion: Postoperative home BP-monitoring was feasible and well-accepted by CEA-patients. Future studies need to address the clinical gain of home BP-monitoring in early detection of patients at risk for postoperative hemodynamic complications.

Introduction

In patients with severe carotid artery stenosis undergoing carotid endarterectomy (CEA), cerebral autoregulation is often disturbed, making cerebral perfusion dependent on blood pressure (BP). Hemodynamic disturbances, i.e. hypertensive and hypotensive episodes, are the believed causative factor for perioperative strokes following CEA in at least half of patients, and may occur up to 30 days after surgery.[1,2] Therefore, tight perioperative BP-control is an essential component of stroke prevention after CEA.

Despite the importance of in-hospital perioperative BP-management, little is known of BP changes in the first weeks after CEA. Self-measurement of BP at home could close this knowledge gap and help to target patients who are most at risk. It might also allow earlier recognition of deterioration and early intervention.

In this pilot study, we asked CEA-patients to perform BP-measurements twice daily at home during the first 30 days after discharge and observed BP remotely. The primary aim was to assess feasibility and patient experiences with daily BP self-measurements. The secondary objective was to gain insight into postoperative BP-trends.

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Methods

Subjects

This study was approved by the local ethical committee (NL59854.041.17, 17-177/D). Written informed consent was obtained in patients undergoing CEA between October 2017 and July 2018 at a tertiary referral vascular center, University Medical Center Utrecht, the Netherlands. Exclusion criteria: Modified Rankin Scale score>2 or no access to wireless internet.

Study design

The study was a prospective feasibility-study including 30 CEA-patients. Since a formal power calculation was not feasible due to the lack of preliminary data, a sample size of 30 was estimated for explorative analysis. Patients received an ambulatory BP monitor (OMRON HEM-9210T, Healthcare CO.Lt., Kyoto, Japan) transmitting BP-values to a secured online dashboard via telemonitoring (Luscii Vitals, Luscii Healthtech BV, Amsterdam, The Netherlands) on an iPad (Apple Inc., Cupertino, CA, USA). Patients were trained to record BP twice daily at rest (morning and evening), for 30 days after hospital discharge. Researchers had access to an online clinician dashboard to review patients' measurements over time. In case of a missing BP-measurement, a reminder was sent. For each patient, a systolic BP upper limit was determined based on the magnitude of postoperative increase of cerebral blood flow measured by transcranial Doppler (TCD). An alert was generated if BP exceeded this threshold with ≥15%. Two researchers (LF and MB) checked the BP-measurements daily. If four consecutive alerts were generated (i.e., exceedance of systolic BP threshold >two days), patients were requested to visit the Vascular Surgery outpatient clinic. At the end of the study, patients' experiences and perceived feasibility of home BP-monitoring following CEA was assessed by a telephone survey. The survey consisted of 14 items divided into four categories; 'Hospital admission' (3 items), 'Perceived health' (2 items), 'Patient experience' (7 items) and 'Usability' (2 items). (Supplemental data, Table 1). Patients' adherence to the monitoring protocol, BP time series, and any interventions were also scored.

The costs incurred for telemonitoring 30 study-patients for one month following hospital discharge were €76 per patient (total:€2280). This includes one telemonitoring month (application and clinicians' dashboard, €13.50pppm), iPad lease (€29.50 pppm) and the acquisition costs of ten home BP-monitors (total:€990).

Statistical analyses

Descriptive statistics were used to analyze the primary outcome and summarize patients' experience and satisfaction measures. Percentage of agreement was calculated by the percentage of patients scoring on a four-point Likert scale.

BP changes, patient adherence, BP time series and number of interventions are presented as mean (±SD) or median (interquartile range), as appropriate, and categorical variables as n (percentage). Intra-individual variability of BP was calculated for each patient over the 30-day monitoring period (±SD). Proportion of hypertensive episodes (BP > systolic upper limit) were calculated.

Subgroup analyses were performed based on the presence of postoperative hemodynamic complications, postoperative admission to a high-care unit and overall postoperative complications. P-value<0.05 was considered statistically significant.

Results

Patient population

Of 42 eligible patients, 34 gave informed consent. Four patients withdrew before the monitoring period started due to postoperative ADL-dependency (n=2) or unwillingness to perform measurements (n=2). In total, 30 CEA-patients (87% males, 68±8 years) completed the BP-monitoring period at home.

Neurological outcome

In-hospital, two patients (7%) developed postoperative cerebral hyperperfusion (TCD>100% increase), one patient had a postoperative bleeding requiring surgery (3%) and one patient suffered a TIA (3%). Five patients (17%) were admitted to a high-care unit for prolonged monitoring of hemodynamic parameters. Post-discharge, four patients experienced an adverse event of which two were hemodynamic events; readmission due to stress-related hypertension and postoperative bleeding requiring surgery (Table 1).

Table 1. Baseline characteristics

	All patients (n=30)
Age	69 (50-93)
Sex, male	26 (87)
Risk factors	
Hypertension	26 (87)
Hyperlipidaemia	19 (63)
Diabetes mellitus	5 (17)
Coronary artery disease	10 (33)
Peripheral arterial disease	9 (30)
Smoker (current/ex)	25 (83)
Symptomatic	27 (90)
Stenosis degree, ipsilateral	
50-70%	2 (7)
> 70%	28 (93)
Stenosis degree, controlateral	
Occlusion	3 (10)
> 70%	6 (20)
50-70%	5 (17)
< 50%	16 (53)
Shunt-use	1 (3)
Medication	
Statins	26 (87)
Antiplatelets	27 (90)
Anti-coagulants	3 (10)
Antihypertensive drugs	24 (80)
≥ 2 drugs	14 (47)
Postoperative events	
In-hospital:	
Post-procedural bleeding	1 (3)
TIA	1 (3)
Post-discharge:	
Post-procedural bleeding	1 (3)
Myocardial infarction	1 (3)
TIA	1 (3)
Stress-related hypertension	1 (3)
BP-related GP visit	8 (27)
BP-related medication change GP	2 (7)

* Data in median (range), or number (%). GP: General practitioner

Patient experience

Patients reported a very positive (57%) or slightly positive experience (33%) with BP-monitoring at home. Usability of home BP-monitoring was found to be 'very easy' by most patients (91%). All except one of the patients would recommend home BP-monitoring as part of the standard of care after CEA. (Figure 1)
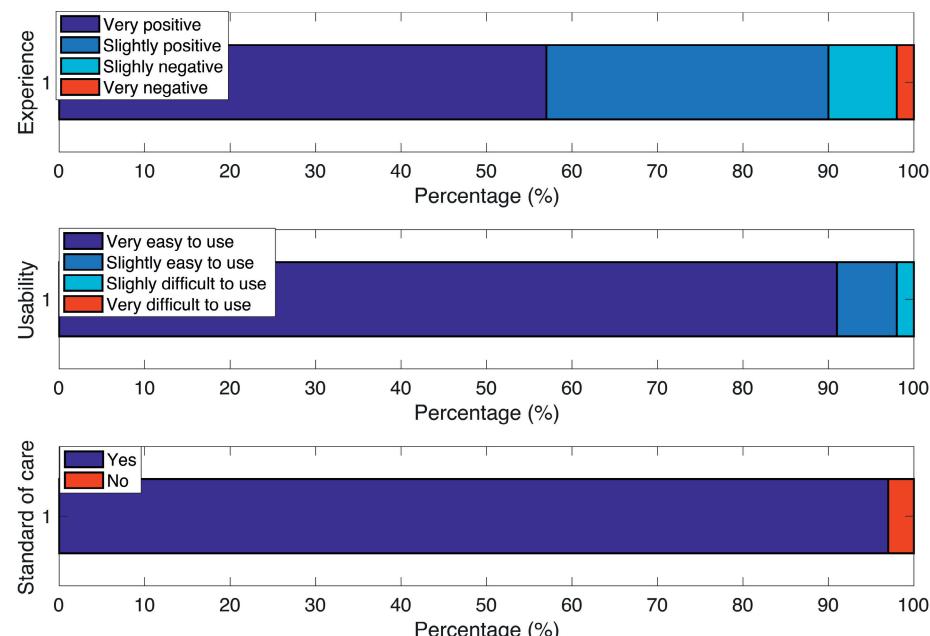
Figure 1. Feasibility of Home blood-pressure monitoring

Measurement adherence

Patient adherence to home BP-measurement was high; 24 patients provided ≥90% of the expected BP-measurements. Home BP-monitoring increased awareness of adequate BP control. Eight patients visited their general practitioner (GP) for concern regarding observed BP-values, leading to changes in anti-hypertensive therapy in two patients.

In 13 patients (43%) there was at least one systolic hypertensive measurement (BP > systolic upper limit) and in 3 patients (10%) BP exceeded the systolic threshold by >15%. However, in none of the patients, four consecutive BP-measurements exceeded the individual systolic BP threshold. The average number of reminders sent to the patient as a result of a missing BP-measurement was 4.2. Median intra-individual variability of systolic and diastolic BP of all patients was 12.7

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mmHg and 7.4 mmHg, respectively. Variability (10.5 vs 13.1 mmHg) and absolute values (136 vs 139 mmHg) of systolic BP-measurements did not significantly differ between patients with an event post-discharge and those without. (Figure 2)
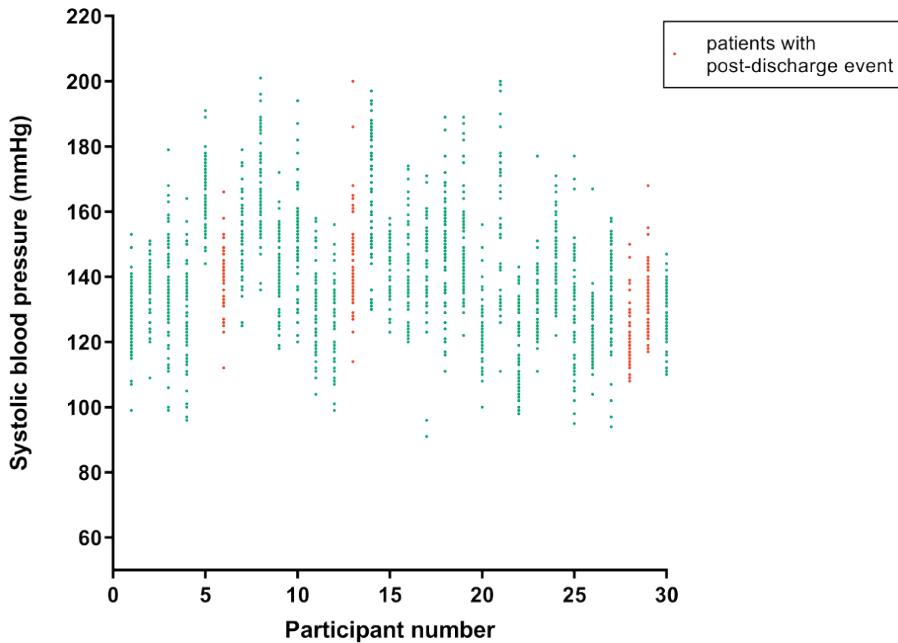
Figure 2. Intra-individual variability of systolic blood-pressure

DISCUSSION

Within this feasibility study, postoperative home BP-monitoring was well-accepted - and even recommended - by CEA-patients. This is the first step towards closing the knowledge gap of BP changes in the first four weeks following CEA. Besides, home BP-monitoring led to increased patient awareness resulting in self-intended visits to GP and BP-therapy changes.

The study design is unique. By implementing home BP-monitoring to postoperative care, we expanded postoperative care to the home setting. This new concept of care enables daily remote monitoring of BP-measurements by healthcare providers with the possibility to intervene, if deemed necessary. Hereby improved quality of care and safety is pursued as well as creating more patient-centered care by active participation and insight in own health.

Over the past years, home BP-monitoring has been shown to improve BP control in hypertension treatment. [3] Although the rise of telemonitoring as a novel approach and an alternative for protocolized follow-up, it is primarily used for chronic conditions while adoption in postoperative care is still in its infancy. [4-6] Implications on cost savings are still largely to be determined.

Use of telemonitoring in a selected high-risk postoperative patient group might reduce the need for outpatient visits or enable the detection of hemodynamic complications in an early stage. If such early detection and intervention could prevent post-discharge neurological complications and prevent hospital readmissions, the benefits of telemonitoring are likely to outweigh costs. In addition, patient satisfaction with postoperative BP telemonitoring was high; higher perceived safety and reduced insecurity is the most likely reason why patients recommended home BP-self measurements after hospital discharge to become standard of care.

Although home BP-monitoring seems suitable for a large group of patients, awareness is needed for possible unintended consequences when patients see their BP-values twice daily. One patient experienced stress because his BP was higher than expected. As a result, stress-related hypertension occurred, and for safety reasons, he was readmitted. However, the overall results show a very positive experience with remote monitoring at home.

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Limitations

First, patients were included in a tertiary referral center which may not represent all CEA-patients. However, only five patients stated that their main reason not to participate was the anticipated burden of BP-monitoring for 30 days. Second, it was not possible to add chosen side per BP-measurement (left or right arm) in the application. This may have influenced the intra-individual BP-variability, regardless of the instruction to perform BP-measurements only on the arm that is known to provide the highest BP readings. Finally, no conclusions can be drawn on our observation of no significant differences in postoperative BP-patterns between patients with and without postoperative events, since the study lacked the necessary statistical power to detect such differences. Therefore, we suggest addressing post-CEA BP-trends, variability and changes compared to preoperative BP as crucial new research questions.

Conclusion

Postoperative home BP-monitoring is well-accepted and even recommended by CEA-patients. Future larger studies need to address the potential clinical gain of home BP-monitoring in early detection and management of patients at risk for postoperative hemodynamic complications.

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Chapter 7

Wireless remote home monitoring of vital signs in patients discharged early after esophagectomy: observational feasibility study

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Abstract

Background: Hospital stay after major surgery is shorter than ever before. Although enhanced recovery and early discharge have many benefits, some complications will now first manifest themselves in the home setting. Remote patient monitoring in the first days after hospital discharge with wearable sensors may capture clinical deterioration earlier, but is largely uncharted territory.

Objective: this study aimed to assess the technical feasibility and experiences of patients discharged home after esophagectomy while being remotely monitored with a wireless patch sensor. In addition, we determined whether observing vital signs with a wireless patch sensor in these patients influences clinical decision making.

Methods: In an observational feasibility study, vital signs of patients after esophagectomy were monitored with a wearable patch sensor (VitalPatch, VitalConnect Inc., San Jose, CA) during the first seven days at home after hospital discharge. Vital signs trends were shared with the surgical team once a day and they were asked to check the patient's condition by phone each morning. Patient experiences were evaluated with a questionnaire and technical feasibility was analyzed on a daily basis as the percentage of data loss and gap durations. In addition, the number of patients in which a change in clinical decision was made based on the results of remote vital signs monitoring at home was assessed.

Results: 20 patients completed 140 days (7 days each) of home monitoring with the wearable patch sensor. Each of the patients had good recovery at home, and remotely observed vital signs trends did not alter clinical decision making. Patients appreciated that surgeons checked their vital signs daily (mean 4.4 / 5) and were happy to be called by the surgical team each day (mean 4.5 / 5). Wearability of the patch was high (mean 4.4 / 5) and no reports of skin irritation were mentioned. Overal data loss of vital signs measurements at home was 25%; both data loss and gap duration varied considerably among patients.

Conclusions: Remote monitoring of vital signs combined with telephone support from the surgical team was feasible and well perceived by all patients. Future studies need to evaluate the impact of home monitoring on patient outcome as well as cost-effectiveness of this new approach.

Introduction

Vital signs monitoring in high-care settings, e.g., the Intensive Care Unit (ICU), includes continuous measurement of different vital signs and frequent visual observations of the patient's clinical status by the nurse. In low care settings, such as surgical wards, the current standard is intermittent measurement of vital signs only, usually once every shift [1,2]. By contrast, in patients discharged home after major surgery, vital signs are no longer monitored at all. Although the risk of patient deterioration decreases towards the day of hospital discharge, the risk that patient deterioration at home will go unnoticed increases.

Nowadays, patients after major surgery are discharged home earlier than ever before. In part, this is facilitated with the introduction of enhanced recovery after surgery (ERAS) programs that have shown to accelerate patient recovery, resulting in shorter hospital length of stay [3-5]. Although recovery within the patient's own home has many benefits, at least some late major complications might first manifest themselves in the home setting. This increases the risk that early warning signs will be missed.

Recognizing the early signs of deterioration in the first few 'critical' days at home might be improved if remote monitoring of vital signs would become available for patients at high risk for complications, such as patients discharged home early after esophagectomy. Hospital readmissions after esophagectomy occur frequently, ranging from 5%-19% and are associated with poor outcomes [3,6-8]. Advances in telemonitoring technology have now resulted in wearable and wireless sensors for remote and unobtrusive vital signs monitoring. Such technology could provide patients the opportunity to recover at home, knowing that the hospital team will capture any possible deterioration early. At least in theory, this should allow safe early discharge after surgery and may reassure patients and their family.

Several studies demonstrated the feasibility of wireless vital signs monitoring in patients admitted to the hospital [9-12], but monitoring patients at home in the first days after hospital discharge with wearable sensors is largely uncharted territory. It is unknown whether it is feasible to monitor patients remotely at home or whether remotely observing vital signs positively impacts clinical decision making.

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Therefore, the objective of this study is to assess the technical feasibility and experiences of patients discharged home after esophagectomy while being remotely monitored with a wireless patch sensor. In addition, we aim to determine whether observing vital signs with a wireless patch sensor in these patients influences clinical decision making.

Methods

Study design and setting

This was an observational feasibility study in which patients after esophagectomy were monitored with a wearable patch sensor (VitalPatch, VitalConnect, San Jose, CA) on the general ward of the University Medical Center Utrecht, the Netherlands, and at home during the first seven days after hospital discharge. The UMC Utrecht ethics committee waived the need of formal ethical approval.

Study population

Patients after esophagectomy receiving care at the surgical oncology ward were included. All patients were informed about the study one week before surgery by phone. Exlusion criteria were known skin allergies, pacemaker or implantable cardioverter defibrillator, or a wound near the application site of the patch. After written informed consent was obtained from the patient on the surgical ward, the wireless patch sensor was applied and vital signs recording started.

Description of the wireless patch sensor

The VitalPatch wearable biosensor consists of a disposable adhesive patch that incorporates two electrocardiography (ECG) electrodes, a tri-axial accelerometer and a thermistor. It is designed to facilitate remote monitoring of patients on the ward as well as in the home setting after hospital discharge. Heart rate and respiratory rate measurements of a previous version of the VitalPatch sensor (the HealthPatch) have been validated in high-risk patients in a clinical environment [13,14]. The patch can be applied on the patient's chest and it records heart rate, heart rate variability, respiratory rate and skin temperature every 4s, body posture and steps for five days continuously. Data was sent via Bluetooth to a mobile phone (Cubot King Kong 3, Shenzhen Huafurui technology Co. Ltd, China), which uploads the data over cellular networks to the MediBioSense HealthStream (MedioBioSense LTD, United Kingdom) cloud platform. This application can display vital signs data in real time, but was not designed to view long-term vital sign trends. Data could be stored for 18 hours on the sensor if connection between

the patch sensor and mobile application gets lost. Hereafter, it takes half of the upload time of the live data to upload this offline-data to the cloud platform. No patient identifiable information was entered on the mobile device or application to ensure compliance with European General Data Protection Regulation.

Data collection

Patients wore a patch sensor on the surgical ward and during the first seven days after hospital discharge. In-hospital measurements were solely used to generate baseline data prior to discharge, and the patient's vital signs were observed intermittently through care as usual. A new patch was applied upon discharge and patients were taught how to replace a new patch after 5 days at home. In addition, they were instructed to keep the mobile phone charged and within a range of 10 m. It was made explicit that wearing a patch at home does not mean that the patient's vital signs will be continuously observed. Instead, their vital sign trends at home were checked once every 24 h.

Each morning, for seven days post discharge, vital signs trends over 24 h and vital sign trends over 7 days were shared with the gastrointestinal oncology surgical team (3 surgeons, two surgical residents, one physician assistant) in a secure medical messaging application (Siilo, Siilo Holding BV, Amsterdam). An example is shown in Figure 1 and 2. Surgeons were asked to check the patient's condition each morning by phone using a short structured format with questions such as 'how do you feel', and asking about pain and fever. Phone calls were used as a safety net to prevent cases of missed patient deterioration, since the added value of remote vital signs monitoring needs to be established first. After each phone call, surgeons scored the patient's condition with a 0 (no cause for concern), 1 (slightly worried) or 2 (significant concern). Conservative wait-and-see treatment was applied if a score of 1 was given and the general practitioner was informed if a 2 was scored. Thereafter, a surgical team member checked the vital signs trend overviews and used that information to reassess their score. An 'X' was scored if not enough vital signs data were available. This approach allowed the surgical team to adapt treatment policy – if needed - after taking into account information from the vital signs data trends.

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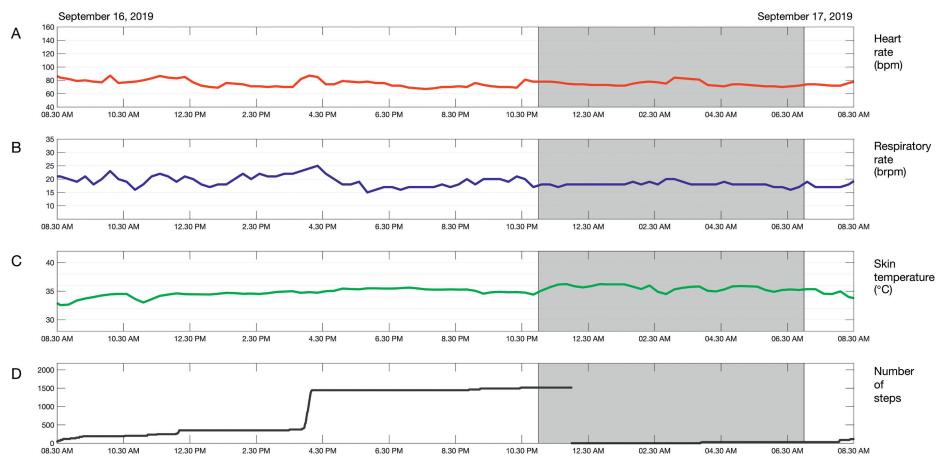
Figure 1. Example with a vital signs trend overview over the last 24 h showing heart rate (red), respiratory rate (blue), skin temperature (green) and cumulative number of steps (black). The shaded area indicates the hours of the night.
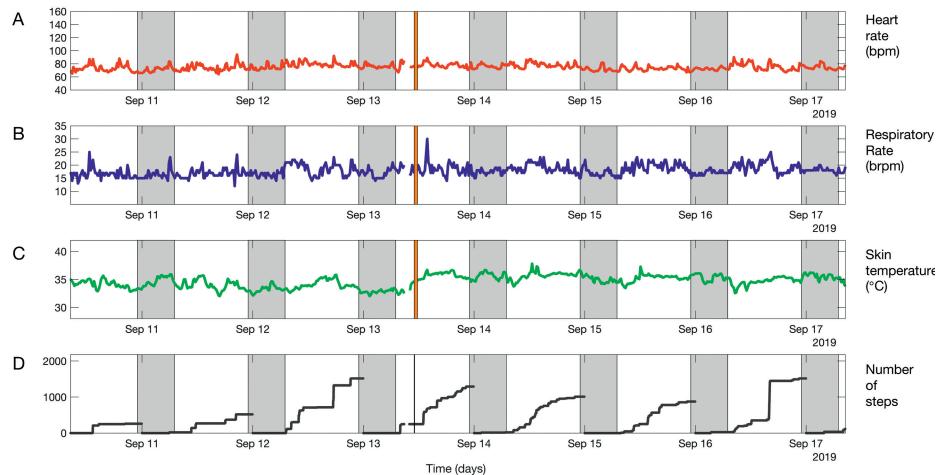
Figure 2. Example with a vital signs trend overview over 7 days, both within hospital and at home after hospital discharge. The orange line indicates the time of hospital discharge. Heart rate (red), respiratory rate (blue), skin temperature (green) and cumulative number of steps (black) are shown. The shaded area indicates the hours of the night.

Signal analysis

Wireless sensor data was retrieved in comma-separated (CSV) text files and stored in a secured local research database. Data reports were processed using Matlab (MathWorks, United States). A median filter over subsequent epochs of 15 min was applied to eliminate artifacts from transients and to increase clarity and 'readability' of the vital signs trend overviews. 'Number of steps' was reset to zero at midnight to allow easy visual verification of the patients' daily activity level.

Outcome measures

Patient experiences of being remotely monitored at home and sensor 'wearability' were assessed with a questionnaire, completed after the study. This questionnaire consisted of 8 questions on a 5-point Likert scale, 2 open answer questions, 1 yes/no question and 1 question with three possible answers. The technical feasibility of remote home monitoring with a wireless sensor was assessed on a daily basis as the percentage of useful data available for vital signs interpretation. In addition, maximum duration of data loss was defined as gap durations with a maximum length of 15 min, 1 h, 1- 4 h, or 4 h or longer. We distinguished data loss as observed between the time of vital signs assessment (each morning) and at the end of the entire measurement period.

Another outcome measure was the number of patients in which a change in clinical decision was made based on the results of remote vital signs monitoring. This was measured by registering the number of times a score was adapted from 0 to 1, or from 1 to 2 following inspection of the vital signs trend overviews and compared with the check of the patient's condition by phone each day. In addition, trend patterns in the first week post-discharge of heart rate, respiratory rate, skin temperature and number of steps were also assessed.

Statistical Analysis

Descriptive statistics were used to evaluate patient demographics and to assess feasibility of home monitoring. Since this was an observational feasibility study not designed to assess whether remote home monitoring can improve patient outcome, we refrained from formal sample size calculation. Given the much lower probability of post-discharge adverse events, very large sample sizes will likely be needed to demonstrate statistically significant differences in outcome.

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Results

Patient population

Patients were recruited from July 2019 – December 2019. Of 29 patients screened, 23 gave informed consent. 6 patients declined to participate, either because they already had 'too much on their mind', did not want to stay connected with the hospital once back home or thought they would not be able to cope with such modern technology. Two patients withdrew before the home monitoring period started because they were no longer willing to participate. One patient died during hospital admission. In total, 20 patients completed 140 days (7 days each) of home monitoring with the wearable patch sensor. None of these patients were readmitted to the hospital within 30 days and only one event after discharge home was observed. Table 1 summarizes patient characteristics.

Table 1: Patient characteristics[a]

	All patients (n = 20)
Age	70 (7)
Sex, male	16 (80)
BMI	25 (2)
Living alone	4 (20)
Comorbidities	
Hypertension	9 (45)
Cardiovascular disease	5 (25)
COPD	4 (20)
Diabetes mellitus	3 (15)
Length of stay (days)	11 (7)
Readmission within 30 days	0 (0)
Postoperative events	
In-hospital	
Pneumonia	13 (65)
Atrial fibrillation	6 (30)
Anastomotic leak	7 (35)
Chyle leak	2 (10)
Pneumothorax	1 (5)
Patients without events	2 (10)
Post-discharge	
Severe dyspnea	1 (5)

[a]Data in median (interquartile range), or numbers (%)

Patient experiences

Patient experiences were collected via a questionnaire as shown in Table 2. Overall, patients reported very high satisfaction rates. They appreciated that physicians checked their vital signs daily and they were happy to be called by the surgical team each day. The wearability of the patch sensor in the outpatient setting was high; patients were not aware of wearing a patch. Furthermore, no reports of skin irritation were mentioned and the patch stayed in place most of the time, even during sweating and showering. One patient lost the patch twice at home, due to excessive sweating. Replacing the patch themselves at home was considered very easy. No information was visible on the dedicated mobile phone that acted as a gateway for the vital signs data, but patients were asked to keep the phone in close approximity to ensure uninterrupted data transmission. Interestingly, 95% of patients reported they did not miss the absence of data on the mobile phone regarding current vital signs values or the proper functioning of the entire system. Only one patient mentioned it would be reassuring to show the vital signs and additional information whether their vital signs data is being transferred to surgeons correctly. 75% of the patients reported feeling safer at home knowing that their vital signs trends were checked and being called by a physician daily.

In addition, all patients were asked to imagine a future scenario in which they would be offered the option to go home one day earlier with a wireless patch sensor. Seventy five percent of patients indicated they would prefer to be discharged earlier with the assistance of a remote patient monitoring solution. The main reasons given for this preference were a belief that they would recover more quickly at home and the fact that it is much more convenient to recover in one's own home than in a hospital bed. A few patients mentioned that they felt quite uncertain to be discharged home after such a major surgical procedure. As one patient noted: 'It is quite a transition from a hospital were they constantly keep an eye on you, to home. If gives you reassurance when you have the feeling that your condition is being checked remotely'. Most of the patients reported the necessity to have home care properly organized and ideally to have the possibility to access home care 24 h a day. Of note, the amount of homecare received by these patients was dependent on their need for assistance with tube feeding or wound care. Three patients did not like the idea of being discharged home sooner with assistance of a remote patient monitoring solution, either because they felt they were discharged quite quickly already, while they were still recovering from adverse events that occurred in-hospital or they had

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experienced that their medications or home care was not adequately organized at the time they were discharged home.

Table 2. Questions on patients' experience of being remotely monitored at home with the VitalPatch sensor. Patients responded on a 5 point Likert scale whether they disagreed (1) or agreed (5), yes/no questions or an open answer.

#	Question	All patients (n=20)
1	How did you experience wearing the patch in the first week after hospital discharge? (mean; scale 1-5)	4.1
2	How did your partner experience the fact that you wore this patch and that your vitals were checked by physicians remotely? (mean; scale 1-5)	4.5
3	To what extent did you find it pleasant or not pleasant that physicians were able to see your vital signs once daily? (mean; scale 1-5)	4.4
4	To what extent did you find it pleasant or not pleasant that physicians called you each day to ask how you were doing? (mean; scale 1-5)	4.5
5	Nothing was visible on this mobile phone you had in approximity. Would you have preferred to see any data on this mobile phone, or you haven't missed this? (% yes)	95
6	Your vitals were checked and you were called once daily. To what extent did this make you feel safer or not? (% yes)	75
7	Imagine you have a choice to go home one day earlier with such a wireless patch sensor in the future. What do you think of this? (% yes)	75
8	What would you need for this, to make yourself comfortable at home? (open answer)	open
9	To what extent were you aware of wearing this patch? (mean; scale 1-5)	4.4
10	To what extent caused this patch irritation on your skin? (mean; scale 1-5)	5
11	To what extent stayed this patch in place, even during sweating and showering? (mean; scale 1-5)	4.8
12	To what extent was it easy to replace the patch at home? (mean; scale 1-5)	4.8

Feasibility of home monitoring

Overall data loss of all vital signs at the time of assessment each morning was 25% (SD: 24%) and 14% (SD: 19%) after the entire measurement period. The amount of data loss varied considerably among patients as can be seen in Figure 3. At the time of patch replacement at home (by the patient themselves), most cases showed a preceding period with data loss. More than 77% of the gap durations at the time of vital signs assessment were less than 1 h, with the majority of gaps lasting less than 15 min. An overview of frequency and duration of data loss is shown in Table 3.

Figure 3. Percentage of available data (green) and data loss (red) of all patients per hour during each day of home measurements. Each star indicates the first measurement of a new patch.

Table 3. Amount of known data loss at the time of daily assessment (around 8:30 AM) and total amount of data loss as recorded at the end of the entire measurement period[a]

	Data loss in the previous 24h (as observed at the time of assessment)	Data loss at the end of the entire measurement period
Overall data loss % (SD)	25 (24)	14 (19)
Number of gaps (%)		
< 15 m	235 (55)	245 (67)
15 - 60 m	93 (22)	66 (18)
1 - 4 h	66 (15)	37 (10)
> 4 h	35 (8)	19 (5)

[a]Data in numbers (%). SD = standard deviation
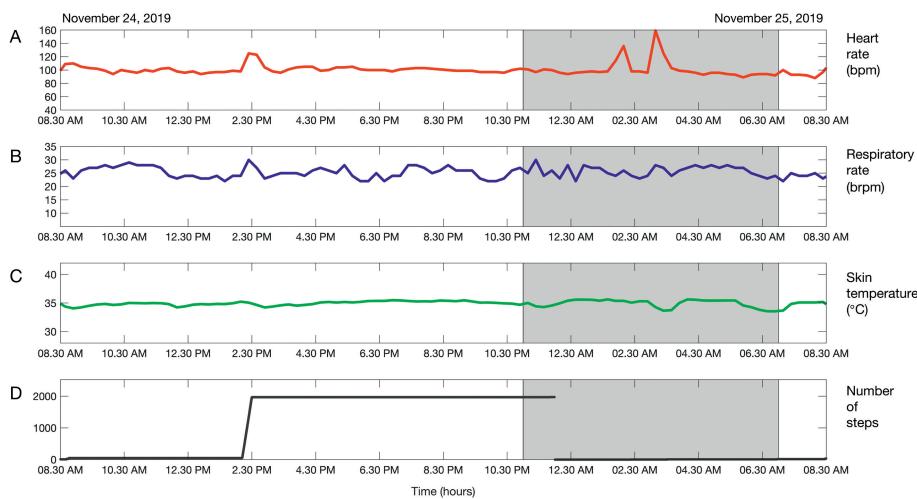
Figure 4. Vital signs trend overview over 24 h of a patient who complained of severe dyspnea and coughing, when called at 08:30 h (end of graph). Two episodes of increased heart rate can be seen during the night, but no clear vital signs deterioration occurred over the last 24 h. Heart rate (red), respiratory rate (blue), skin temperature (green) and cumulative number of steps (black) are shown. The shaded area indicates the hours of the night.
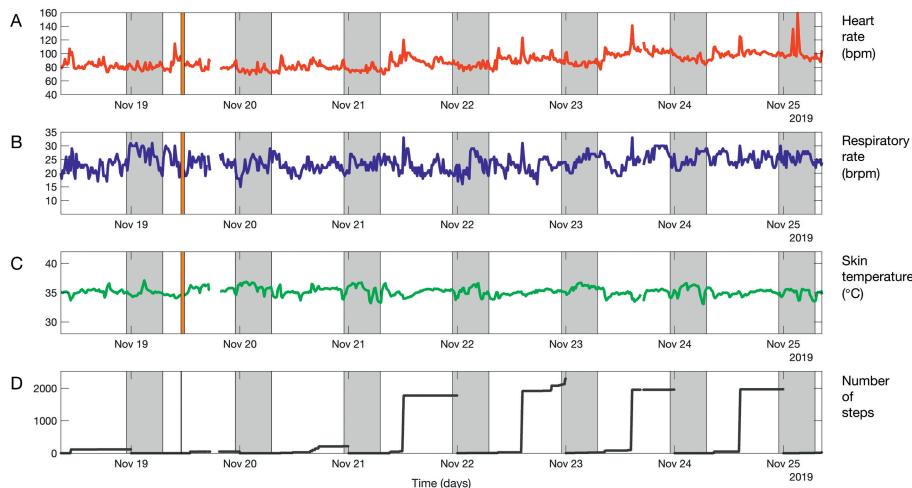
Figure 5. Vital sign trend overview over 7 days of the patient who complained of severe dyspnea and coughing on November 25th. The orange line indicates the time of hospital discharge. Until November 22th, heart rate fluctuated around 80 bpm at night and most respiratory rate values remained between 20 and 25 brpm. From November 22th until November 25th, heart rate slowly increased from 80 to 100 bpm at night, while respiratory rate slightly increased to 25-30 brpm on November 23th. The surgical team member asked the general practioner to check the patient at home and prescribed bronchodilator treatment. Heart rate (red), respiratory rate (blue), skin temperature (green) and cumulative number of steps (black) are shown. The shaded area indicates the hours of the night.

Scoring of vital signs trends in patients at home

Table 4 shows an overview of scores provided after each call and vital signs observations. In four (3%) occasions, the surgeon was slightly worried about the patient's condition after the phone call, but this did not result in an increased score after checking the vital signs trend overviews. As a result, clinical decision making was not changed based on observing vital signs. During one phone call the patient complained about severe dyspnea and coughing, after which a score of 2 ('concern') was given and the general practitioner was asked to check on the patient's condition and prescribed bronchodilator treatment. However, the vital signs trend overviews were not scored as worrisome (Figure 4 and 5). Although no clear diagnosis could be found at this point in time, this patient continued struggling and was admitted to the hospital with atelectasis four weeks later. On eight occasions (6%), a score of 1 ('slightly worried') was assigned after checking the vital signs trends, most ofen related to a high heart rate at rest shortly after hospital discharge. Overviews of vital sign trends were not available on 9 (6%) occasions due to data loss.

Table 4. Overview of scores after phone calls and vital signs observations

Observation	Value, n %)
Number of phone calls	137 (98)
Number of missed calls	3 (2)
Phone calls	
Slightly worried score '1'	4 (3)
Concerned score '2'	1 (1)
Vital signs observations	
Slightly worried score '1'	8 (6)
Concerned score '2'	0 (0)
Unable to judge 'X'	9 (6)

Observing vital sign trends over time

Figure 6 provides an overview of the averaged heart rate, respiratory rate and skin temperature during night-time hours (11pm – 7 am) in the four days before hospital discharge until the first seven days at home. Heart rate decreases from 89 bpm in-hospital to 85 bpm at home, whereas no change in average respiratory rate is visible between the hospital and home period. Overall, high variation in heart rate and respiratory rate among patients at night can be seen. Skin temperature slightly increases in the first days at home. Figure 7 shows a boxplot of the number of steps in the first seven days after hospital discharge. The

average number of steps increased from 500 to 1300, suggesting that patients' daily activity increases gradually as recovery progresses at home.
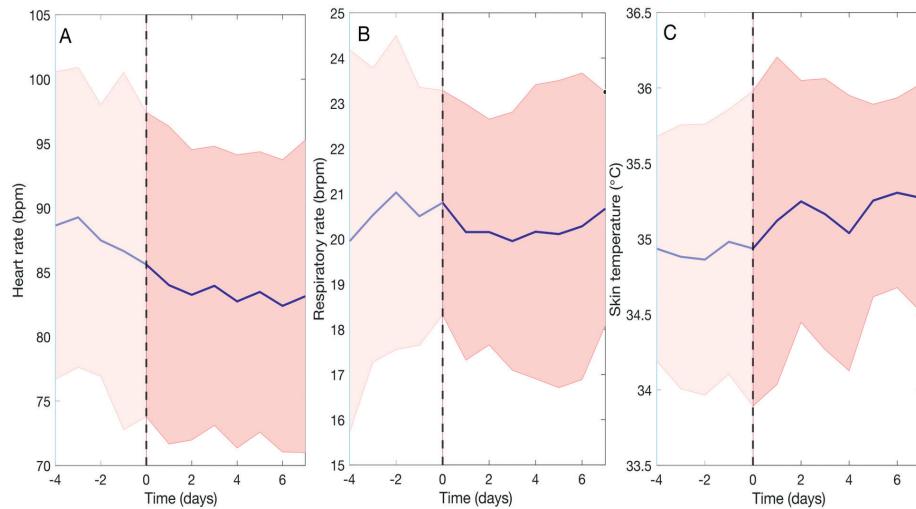

Figure 6. Mean (blue line) and SD (shaded red area) during night-time hours (for a period starting 4 days before hospital discharge until 7 days after discharge) of (A) heart rate, (B) respiratory rate, and (C) skin temperature of all patients.
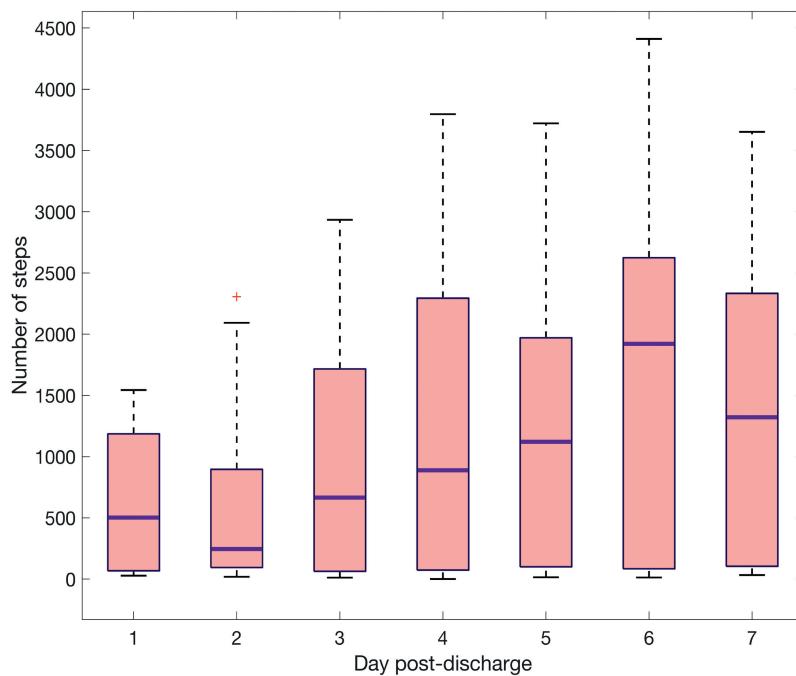

Figure 7. Box plots showing average daily number of steps for the first seven days after hospital discharge.

Discussion

Principal findings

We have investigated the feasibility of remote vital signs monitoring with a wireless patch sensor in patients after esophagectomy in the first week home after hospital discharge and assessed patient experiences. Each of the twenty patients that were monitored at home had good recovery, and remotely observed vital signs trends did not directly alter clinical decision making, although it supported the clinical judgments regarding the patients' condition as derived by the surgical team from the patient's comments during the daily phone calls. In general, remote home monitoring was well perceived by patients and reported satisfaction scores and usability rates were very high. For the sensor used in this study average data loss of vital signs measurements at home was 25%; both data loss and duration of data gaps varied considerably among patients. In this select group of patients recovering from major surgery, we observed a progressive decrease in heart rate and an increase in number of steps during the first seven days at home.

Strenghts and limitations

When interpreting the findings of this study, some limitations should be taken into account. Based on previous studies, we had anticipated a 10% readmission rate in patients after esophagectomy [8,15]. However, we observed only one event after discharge at home and none of the 20 study participants were readmitted to the hospital. Only much larger studies can demonstrate how vital signs trend patterns vary among patients with and without clinical deterioration after hospital discharge. As a result, we were unable to determine whether observing vital sign trends remotely changes clinical decision making. However, we cannot entirely eliminate the possibility that patients who decided to participate in this study had a better baseline prognosis or that a 'Hawthorne effect' (the awareness of being observed remotely and daily phone contact with the surgical team) had positively influenced study outcomes [16,17].

A second limitation is our inability to disentangle the causes of the positive patient experiences. Both the fact that the patient's vital signs were remotely checked and their daily telephone contact with a surgical team member might have contributed. In any case, patients highly appreciated being remotely monitored at home and having daily contact with the team, and as a result, they felt more reassured. Studies have shown that structured telephone calls

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following discharge could even reduce readmission rates in elderly patients [18]. Although these findings cannot be translated to the present study, it seems likely that the ability to communicate with a patient to verify the presence of any deteriorating symptoms, together with abnormal vital signs, may improve recognition of patient deterioration in the home setting.

A score of 1 ('slightly worried') was assigned in 6% of the vital signs trend reviews, most often related to a higher heart rate, especially shortly after hospital discharge or due to high respiratory rates. Elevated heart rate levels – possibly related to the process of recovery and postoperative fatigue – have been noticed before after major surgery [19]. We observed that average heart rate slightly decreased in the days following discharge home. In contrast, average respiratory rate remained high in these patients monitored at home. One possible explanation could be technical in nature since the measurement approach in this particular sensor tends to overestimate respiratory rate. In a previous study we validated a precursor of the VitalPatch sensor in surgical patients and observed considerable overestimation of respiratory rate [13,14]. Carefully performed validation studies in clinical practice are therefore of crucial importance for a sustainable long-term implementation of remote wireless monitoring [20].

Nobody knows how often one should measure a full set of vital signs in patients discharged home after major surgery. The VitalPatch sensor used in this study measures each of the vital signs in a nearly real-time fashion. This seems redundant for measuring patients in a home setting who are no longer at high risk for deterioration, and may increase the rate of false alarms. In addition, transmitting these continuous data streams consumes valuable energy, and may easily contribute to data loss. In the present study, 35 (8%) of the data gaps were longer than 4 h which may result in difficulties to interpret vital signs trends appropriately. This high number of long duration data gaps is possibly related to the data transmission protocol of the mobile application used in this study. Data could be stored for 18 hours on the patch sensor if Bluetooth connection was transiently lost, but it took an additional 50% of time on top of the upload time of the live data to transfer this 'offline' data to the cloud platform. Although this data transmission protocol could be improved, it is unknown to what extent the duration of such data gaps results in the inability to capture clinical deterioration on time in the home setting. However, it seems likely that a reduced monitoring frequency might be a necessary trade-off to minimize the number of alerts due to missing data. As soon as an alert is generated, a dedicated 24/7 medical call-centre could initiate video communication, for example, to verify the presence of

any signs that might give reason for rapid medical attention and exclude trivial causes for the alert such as exercise. These approaches are especially relevant since the majority of patients at home will not deteriorate, but may develop unimportant vital signs abnormalities which should not trigger intervention.

Comparison with prior work

Studies that evaluate the feasibility and patient experiences of remote home monitoring are limited. A recent study of Tonino et al. demonstrated high wearability and good usability of the VitalPatch sensor worn by a small number of patients in the outpatient setting receiving blood cell transfusions or immunotherapy [21]. The results of the present study confirm these findings. Another study of Selveraj et al. reported high wearing comfort of the HealthPatch sensor in senior participants after long-term monitoring of 50 days in their home setting [22]. Although such studies hint at the convenience of wireless monitoring of patients in the home care setting, these results were obtained in healthy volunteers and may therefore differ when used in patients discharged home.

Despite the fact that 'hospital-to-home' initiatives are still in its infancy, the increasing pressure from payers force hospitals to develop less-expensive alternatives to hospital care. A recent randomized controlled trial compared direct costs of acute care in patients admitted to an emergency department who were randomized to either usual hospital care or hospital-at-home care while vital signs were continuously monitored via the HealthPatch sensor [23]. Although with 20 patients small in size and recruited within a highly selected patient group, the authors found that patients who received hospital-at-home care were readmitted less frequently within 30 days (7% vs. 23%) and their healthcare costs were 38% lower on average. Nonetheless, large well-controlled studies in patients at risk for deterioration are needed to evaluate the impact of remote monitoring on patient outcomes.

Conclusions

A daily 24h vital signs trend evaluation combined with a phone call from the surgical team was feasible and highly appreciated by all patients. The minimal requirements regarding optimal measurement frequency and data continuity for adequate home monitoring need to be further investigated. Remote patient monitoring at home is feasible. Future studies need to evaluate the impact of home monitoring on patient outcome as well as the cost-effectiveness of this approach.

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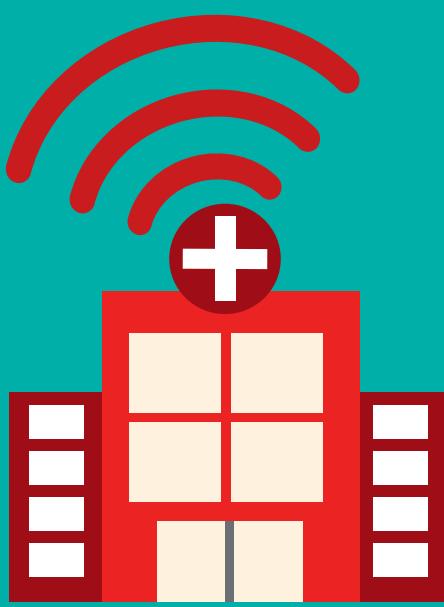
PART 3

An organizational perspective on remote patient monitoring from hospital to home
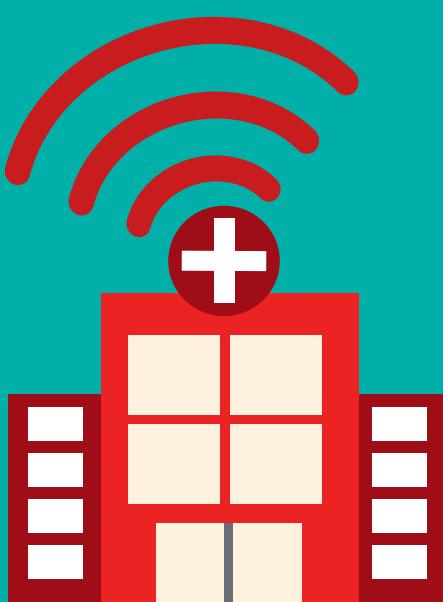
Chapter 8

Conceptual design for remote patient monitoring on the ward and at home after discharge: a Value Sensitive Design approach

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Abstract

Background: Intermittent nurse observations are the current standard on hospital wards so early signs of deterioration may be easily missed. Integrated wireless monitoring systems that allow early detection of deterioration of patients on the ward and at home are currently being developed. It is known that the design choices of medical technology influences the perspectives of users. However, one problem that faces innovations after they become commercially available is that patients or doctors may decide not to use the system, because it is not sufficiently tailored to their needs.

Objective: This study aimed to elicit the values and perspectives of key stakeholders on the potential utility and risks of wireless patient monitoring in the hospital and at home. Knowledge of these stakeholder views can guide important design choices during the development of such systems.

Methods: we selected a theoretically grounded approach: *value sensitive design*. Several steps were taken, starting with a literature-based overview of benefits and risks of wireless patient monitoring within hospital and home settings and identification of a number of key values. Subsequently, we organized focus groups with direct stakeholders in two European countries. Transcripts of focus group discussions were thematically analysed and operationalised into topics and design options.

Results: Four focus group meetings, with in total 18 nurses, 5 patients, 4 relatives and 6 junior doctors were conducted between February 2018 and January 2019. Six topics were discussed most often regarding, usability, alarm strategy, clinical judgment, personal contact, reassurance and reliability. Communication and personal contact between health professionals and patients or relatives and sophisticated alarm notification systems were found to be key design options to ensure successful implementation of remote monitoring.

Conclusions: Incorporating stakeholder perceptions within a value sensitive design approach is essential to anticipate potential problems and to enable early formulation of design options that will facilitate the development and future uptake of systems for wireless patient monitoring.

Introduction

Patient monitoring in 'low-intensity care' environments such as hospital wards is generally limited to intermittent nurse observations and manual measurement of vital signs such as respiratory rate, heart rate and blood pressure [1]. Early signs of patient deterioration can easily go unnoticed for several hours, or are not detected at all [2-4]. This leads to delays in treatment which are associated with additional morbidity and mortality [5,6]. Increasing the intensity of observations and vital signs measurements by more frequent nursing rounds is unlikely given the growing shortage of nurses and the increasing demand for healthcare [7,8]. In addition, hospital lengths of stay are shorter than previously; and although recovery at home has many benefits, unrecognized critical instability and mortality after discharge still occurs [9,10]. This increases the need for reliable, user-friendly early warning systems that can rapidly detect patient deterioration and enable timely treatment.

In the collaborative EU-funded 'Nightingale' project (www.nightingale-h2020. eu), five European academic hospitals (in Utrecht, the Netherlands; Stockholm, Sweden; London, United Kingdom; Leuven, Belgium and Aachen, Germany) invited European industry to develop unobtrusive wearable wireless patient monitoring systems able to predict and detect critical instability of patients both on the general ward and at home after hospital discharge.

A problem for developers of new medical technology is that patients and doctors may decide to stop using the product - or not use it at all - if it is not sufficiently tailored to their needs [11]. To avoid this outcome, we employed the so-called *value sensitive design* (VSD) approach to elicit stakeholder values and views on remote wireless patient monitoring systems [12,13]. VSD allows manufacturers and engineers to identify potential value conflicts early in the design phase to reduce usability difficulties or other problems before a product is launched [14]. It is an iterative process, with conceptual and empirical components. Our aim was to obtain key stakeholder values and perspectives of the different wireless patient monitoring systems developed in the Nightingale project and to use that information early in the development cycle in order to guide product development. In this paper we describe critical elements of VSD and the results of focus group sessions with key stakeholders on the benefits and risks of wireless patient monitoring, both in the hospital and home setting.

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Methods

Based on existing literature on previous VSD research, we identified key values that might play a role in the design of wireless systems for patient monitoring [15,16].We then categorised potential benefits and risks of using wireless patient monitoring systems in hospital and at home with those key values structuring the analysis (Appendix 1).

Subsequently, focus group sessions were conducted to elicit perspectives and viewpoints of direct stakeholders with regard to their values and related understanding of benefits and risks. Focus groups are widely used and proven to be especially useful in this type of health research and development [15].

Participant sampling

Four groups of direct stakeholders: patients, nurses, informal caregivers and doctors were identified. We chose to recruit junior rather than senior doctors since the juniors are much more often present in the hospital 24/7, are tasked with direct patient care during nights and weekends, and are generally the first responders when a nurse is concerned about a patient's condition. The personal network of the authors functioned as 'key gatekeepers' who were invited to recruit their peers, especially nurses and doctors [15]. Patients and informal caregivers were recruited at an organized annual event for patients with esophageal cancer. These patients belong to the target population, since they have experience with recovery after major surgery and might benefit from remote wireless monitoring on the ward or at home in the future.

Data collection

Focus group sessions were conducted in Utrecht, the Netherlands, and Leuven, Belgium, between February 2018 and January 2019. Each session had the same structure with the same sequence of steps: (1) an explanation of the scope of the Nightingale project, (2) a free 'open' period where participants' perceptions of benefits and risks of wireless monitoring systems were discussed, and (3) a semi-structured period to discuss their views on topics that had not yet been addressed based on the overview of values, benefits and risks synthesised from the literature (Appendix 1). All focus groups were moderated and observed by two qualitative researchers involved in the Nightingale project with a background either in ethics, (technical) medicine or nursing. They ensured that all predefined topics identified in the framework overview were discussed and made notes

during the sessions. Each focus group session lasted approximately 90 minutes and was carried out in quiet private rooms. Each session was audio recorded and transcribed verbatim.

Data analysis

Transcripts from all focus group sessions were coded by the first author (MB) using NVivo version 12 (QSR International, Melbourne, Australia). To ensure validity of the coding process, each transcript was also coded by a second researcher (GvT). Discrepancies regarding coding were discussed and resolved by MB and GvT. Subsequently, codes were categorised and themes identified. The qualitative analysis was an iterative process in which topics and explanations are derived from bringing together theoretical insights (in this case the values identified in the literature) and empirical observations. In turn, these empirical observations were the basis for further operationalisation of critical values into design options for the wireless patient monitoring systems. This approach has been termed 'abductive analysis' [17].

Ethics

Before participation, all participants were informed about the purpose of the study through an oral presentation. Informed consent was given verbally. These focus groups are exempt from review by a Medical Research Ethics Committee.

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Results

Focus groups with direct stakeholders

Four focus group sessions with stakeholders were conducted between February 2018 and January 2019. Two focus groups consisted of 9 nurses each, one group comprised of 5 patients and 4 caregivers and the fourth group comprised of 6 doctors (see Table 1).

Table 1. Focus group meetings overview

	Nurses (n)	Patients[a] (n)	Caregivers[a] (n)	Doctors (n)
University Medical Centre Utrecht (Utrecht, The Netherlands)	9	5	4	6
University Hospitals Leuven (Leuven, Belgium)	9			
Total	18	5	4	6

[a] Focus group meetings with patients and carers were held together

Six topics emerged from the abducted analysis which reflect the most important aspects of the systems in question as perceived by the participants. We present each topic in more detail and illustrate this with quotations below.

Usability

The term 'usability' was used to describe the learnability, ease of use, and comfort when wearing of the wireless patient monitoring systems under review. Patients stressed the importance of having sensors that are comfortable to wear, preferably without any wires or tubes, saying that they may become frustrated or start to feel anxious and stressed if sensor systems were too complicated,. Two different opinions emerged according to the different needs of patients. 'Active' patients would like to be involved in their care as much as possible. They prefer to actually see and understand their own vital signs when being remotely monitored. In contrast, 'passive' patients expressed no desire to track their condition themselves; saying that "too much" information would actually make them anxious and that they would prefer to rely on the health professionals. This latter group of patients may be unnecessarily burdened if the system requires that the patient always has an active role in the monitoring process.

Nurses understood usability in terms of remote monitoring leading to improved working conditions and less administration. They also wanted to be able to

immediately interpret a patient's status. One individual emphasised the role of usability saying:

"It all comes down to ease of use and whether the system is comfortable in use, or whether it limits you in daily practice" (nurse)

Alarm strategy

This topic concerns the relevance of a smart notification system to effectively signal clinical deterioration in patients to health professionals with few if any false alarms. Although early identification of clinical deterioration is one of the most important benefits of implementing remote patient monitoring, nurses warned that they would not be able to check the patient every time if they are exposed to an excessive number of alarms from multiple patients. To prevent false alarms, nurses believe that alarm settings need to be adaptable to a patient' individual needs and current condition, for example, by setting a lower threshold value for oxygen saturation alerts in patients with chronic obstructive pulmonary disease; but also suggest that there are standard default settings available as always setting alarms individually may be too time consuming to do for every patient at every encounter.

"It is important that you - as a care professional - when notified of an alarm condition, can adapt the alarm setting" (nurse)

Junior doctors fully agreed with the risk of too much alarm exposure, but at the same time warned that a smart algorithm intended to avoid false alarms might overlook impending patient deterioration.

"We do not want that an algorithm classifies a patient as' stable', while in fact there is something wrong with this patient" (junior doctor)

Patient participants valued 'reliability' highly and worried that the technology might fail to monitor them properly. False alarms were mainly problematic for patients in that they could unnecessarily upset them.

Clinical judgment

According to nurses, clinical judgment is critical in their work; that is, the opinion or conclusion reached following direct patient observation. Nurses explained that they need to communicate and interact with patients to be able to interpret any deviations in vital signs, and that a likely risk of remote assessment is that

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it eliminates the 'gut-feeling' or clinical judgement derived from direct patient contact. Current ways of working enable the nurse to use his or her clinical judgment skills to confirm whether or not there is genuine cause for concern. Although remote monitoring should generate patient benefit (as a result of more timely notification and response in cases of patient deterioration), nurses perceived there to be a risk when systems incentivise nurses to assess the situation without direct observation. Nurses warned that – because they would be able to see the vital signs outside a patient's room - they might incorrectly believe that seeing "normal" vital signs meant that they can safely miss out their usual patient rounds.

"What I perceive as a risk is that you always need to [actually] see the patient while you're doing the observations" (nurse)

Personal contact

All stakeholders emphasised the importance of personal contact especially when a patient is being remotely monitored at home (e.g., by phone/video). Patients need to trust they will be contacted if a health professional receives a notification about a significant abnormality. Furthermore, patients do not want to feel that they will have to 'fight' for a response if they want to contact a health professional. This may be a particular risk for 'passive' patients that are reluctant to initiate contact from home when they do not feel well, because they would expect themselves to be called by a health professional in case of worrisome signals. Some patients thought that home monitoring carried an increased risk of reduced personal contact, because the monitoring strategy is dependent on computer algorithms, and recommended scheduling formal contact moments to guarantee communication with a health professional via phone or video.

"It is great when you can contact your doctor from home and that you can explain your problems from home" (patient)

Nurses also warned that they would resist implementation of remote monitoring if it would transform their working environment into a high-care 'monitoring ward'. In their view, the sensor system should only function as a back-up means to alert the nurse when a patient deteriorates and needs attention.

Reassurance

Reassurance takes place within the dynamic relationship between a health professional who has the intention to reduce worry and the patient who is

concerned. Patient participants mentioned that they would feel more reassured if they knew that they were being closely monitored, especially in the first days after discharge home. This could reduce their stress and anxiety, and also that of their relatives. For nurses, the proposed systems could provide trust and confidence for them regarding the timely detection of patient deterioration in between nursing observations.

"A safer feeling when you're working at night" (nurse)

Doctor participants on the other hand, were reluctant to leave the detection of patient deterioration to a 'smart' algorithm. All stakeholders believed that the use of remote patient monitoring might cause a false sense of security. Doctors mentioned a particular pitfall: that it might be wrongly thought safe to care for sicker patients than usual on a ward equipped with wireless monitoring, for example, when there are no free beds available on a high-care unit. Patients feared they might put too much trust in the systems instead of trusting their own body signals. The fact that the hospital would want to monitor patients after discharge home was also seen as a sign that the hospital professionals might not be certain about the degree of recovery and therefore wish to keep an eye on them.

"I had a quick recovery during my hospitalization and I felt well when I was discharged home. For me it would create an unnecessarily unsafe feeling when the hospital would have sent me home with this device, rather than the message – you're on the right track" (patient)

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Responsibility

The topic responsibility concerns the question of how responsibility of caregivers will be distributed if remote patient monitoring is introduced on the hospital ward and at home after discharge. Nurse participants feared that using the proposed monitoring systems on the general ward would encourage intensive care doctors to discharge patients from the intensive care unit prematurely, leaving it to the ward nurses and monitoring systems to detect subsequent problems.

"I perceive as the greatest danger that the patient is being discharged from the ICU to the ward too soon" (nurse)

In addition, concerns were raised that remote patient monitoring will be misused by hospital management as a solution for staffing shortages. Nurses also

mentioned that they would need to be able to justify when they responded to an alarm by seeing a patient - or not - for example, because they thought the alarm was spurious or because they had a more urgent task to address. If something goes wrong with the patient, how would these actions be viewed in terms of responsible professional conduct? Doctors believed it is of utmost importance to make clear beforehand which actions and/or interventions must be initiated when the system indicates physiological deterioration, and by whom. Patients differed regarding the desirability and feasibility of self-management. Some patients and caregivers thought that it is the hospital's responsibility to ensure a timely response in case of deterioration or technical issues. Others patients indicated that it ought to be their responsibility to contact the health professional. With respect to who should perform follow-up of patients discharged home, ward nurses insisted that remote monitoring of their former patients after discharge home is not and should not be part of their job, and stressed the need to set up dedicated 'medical observation centres' with specialised nurses who can monitor and contact patients at home if necessary.

Operationalisation of values towards design options for remote wireless patient monitoring

As a next step, we further analysed the six themes that emerged from the focus groups and arrived at four key elements to account for in the design. These design options can be used to guide the development of both wireless monitoring systems and the structures of the care pathways needed to ensure remote monitoring will be safely and effectively implemented.

Key design option 1: A sophisticated analysis and alarm generation system

Remote wireless monitoring systems need to use a combination of sophisticated algorithms to reduce the number of false alarms. Patient movement is the most frequent source of vital signs artefacts, so at a minimum, the devices should take into account whether a patient is resting or actively moving and automatically use that information to weigh the alarm condition before triggering a notification. Moreover, a balance between reliability and reduction of false alarms should be achieved through the option of adapting alarm settings according to individual patient's characteristics and current monitoring needs as appropriate.

Key design option 2: Scheduled contact moments with a patient at home

Early discharge home from hospital may leave patients with many unanswered questions, even when they are at home with a remote monitoring system. Patients stressed that implementing such systems should also include scheduled contact

moments for patients to talk directly with a health professional (via phone or video), at least in the early days after discharge.

Key design option 3: Mandatory face-to-face contact

According to our nurse participants, to prevent situations where a nurse might be tempted to skip patient rounds and to protect the value of nurses' clinical judgment of patients, face-to-face contact as part of routine observations needs to be made mandatory. The wireless monitoring system should therefore incentivise nurses to enter patients rooms to complete his or her observations and to document and communicate any 'nurse worry'. This also enables nurses to demonstrate that they have actually 'seen' the patient if something goes wrong.

Key design option 4. Supportive system for ward staff

The wireless monitoring system should support nursing staff to make clinical decisions that improve patient outcome. It needs to function as a back-up system rather than turning general wards in to critical care units. The nurse needs to have immediate access to a complete overview of a patient's condition on a handheld device or computer if they receive an alert. For patients being remotely monitored at home, a monitoring service in the form of a medical observation centre staffed with trained personnel needs to be established from where caregivers and/or informal carers can be alerted in case of patient deterioration.

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Discussion

The current study explored perceptions of direct stakeholders regarding the development and implementation of remote wearable wireless patient monitoring systems, both in hospitals and at home. Our analysis resulted in four design options that are key for successful adoption of this important innovation in healthcare, emphasising that particular thought is required to ensure that direct personal contact between health professionals and patients is not lost. The necessity of smart algorithms and a sophisticated alarm generation system to prevent frequent false alarms was also repeatedly stressed by all stakeholders. These findings indicate that attention is needed to both specific aspects of the design of wireless monitoring systems, and to the structures and procceses of associated care pathways to ensure remote monitoring will be successfully implemented.

The issues of a high frequency of clinically irrelevant alarms have been widely studied in intensive care and is known to be a significant problem [18-20]. The results of our study confirm a fear about frequent false alarms should continuous remote monitoring be instituted on general wards. It must be realized that a large number of false alarms could be particularly disruptive in the ward setting and at home, especially when there is a low nurse to patient ratio (e.g., at night on the ward) or when there are no nurses around (at home). Our nurse and junior doctor participants suggested that this could rapidly lead to unworkable situations and a reduced vigilance of health professionals to system alerts that might result in delaying responses to alarms from patients in real need of attention. Numerous strategies for the reduction of frequent false alarms are proposed in the literature, such as filters to eliminate technical alarms [21-23] or methods based on artificial intelligence (AI) [24]. However, most of the proposed solutions were developed in simulated environments and have not been tested in real-life clinical settings. Sophisticated alarm generation systems (with or without use of AI) also requires the availability of well-annotated patient data when used outside high-care departments. Moreover, implementation of AI models raises complex legal questions regarding health professionals' liability, particularly if decisions based on AI are not verifiable by a doctor [36]. Consequently, fear of doctors to miss any patient deterioration could prevent health professionals' from using sophisticated clinical decision support systems.

The results of the present study underscore the importance of retaining face-to-face contact between patients and caregivers when implementing remote patient

monitoring protocols. This will allow nurses - and doctors - to add their clinical judgments to the appraisal of a patient's condition even when continuous vital signs can be wirelessly obtained without manual intervention. This finding is in agreement with previous studies showing that a nurse's 'worry' or concern may precede actual patho-physiological changes in vital signs [25-27]. Therefore, although continuous wearable wireless vital signs monitoring may reduce the burden of manual vital signs recording for nurses, one potential unintended consequence of reduced nurse-patient contact is that more subtle patient deterioration could be missed. Consequently, a wearable monitoring system that solely relies on vital signs data will not be maximally effective in predicting patient deterioration if no analysis of subjective intuitive reasoning ('context information') is integrated in the design of the sensor system [27]. Moreover, the critically important sign of altered consciousness is very difficult if not impossible to obtain via the monitoring systems proposed, so interactions between health professionals and patients to capture changes in mentation are essential for this aspect alone.

The inclusion of health professionals' 'worry' or concern is even more important when unsupervised vital signs monitoring takes place in a patient's own home. A recent study found reduced readmission rates through implementation of a discharge follow-up telephone service [28], and although these findings cannot be directly applied to the present project, patients and informal carers did indicate that they feel more reassured when contact moments are scheduled, especially during the first days after discharge home. Two other studies reported on the role of informal carers that could provide important sources of information in alerting nurses to deteriorating patients [29,30]. It therefore seems likely that communication with a patient or relative at home can help provide the necessary 'context' to either validate or dismiss remotely obtained abnormal vital signs and thus improve the specificity of recognizing patient deterioration in the home setting.

Examples of studies that incorporate a multi-stakeholder approach during medical device development are scarce [16,31]. Most studies elicit values and opinions of end-users only after the technology has already entered the market. However, although an appreciation of the importance of patient engagement during the design and regulatory process of medical technology is slowly gaining traction [32,33], involvement of direct stakeholders early in the design of new products is still rare. This may be one explanation for the limited or failed uptake of innovative technology often seen in this sector.

Some limitations need to be considered when interpreting the results of this study. The VSD approach used here did not yet include a technical investigation of the use of the proposed systems in real clinical practice since this medical technology is still in development [34,35]. It is therefore not possible at this stage to measure the actual added value of incorporating a multi-stakeholder VSD approach throughout the development of wireless patient monitoring systems. Nevertheless, the fact that our design process takes into account the perspectives of all direct stakeholders might reduce usability problems or other value conflicts after this technology is launched. A second weakness is the fact that conducting focus group research is less suitable for recruiting representative samples of the population when compared to other methods for qualitative research. The results are therefore exploratory in nature, but are likely to provide at least some important perceptions of all direct stakeholders involved in the development and deployment of remote wireless patient monitoring.

Conclusions

Exploring stakeholder perceptions provides valuable information about potential benefits and risks of introducing new medical technology which can also be translated into design options. Addressing essential design aspects early in the development of new technology will likely improve the innovation process and remove barriers for uptake of new systems. Personal contact between health professionals and patients or relatives, appropriate distribution of responsibilities and a sophisticated alarm notification system were perceived to be key elements of successful implementation of remote monitoring. These insights provide a valid basis to further develop and implement wireless patient monitoring systems both in the hospital and at home after discharge.

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Chapter 9

General discussion

A hypothetical, but possible scenario today

The new coronavirus pandemic is raging around the world. In the Netherlands, the spread of the virus seemed under control, but a second wave is already looming. After reading the newspaper this morning (Box 1), Maria Boerhaave, the chairman of the executive board of an academic hospital in the Netherlands wonders whether they 'need to do something' with remote patient monitoring to manage the COVID-19 pandemic. Could they implement such a safe pathway from ICU to home with wireless and wearable technology within the next year in her hospital? She knows a technical physician who performs research in this field and calls her to ask for advice. What follows hereafter is a discussion to outline the lessons learned and the possibilities to implement remote patient monitoring from hospital to home.

Box 1. *A Dutch hospital uses wireless sensor technology to monitor COVID-19 patients on the ward and to discharge patients earlier to their own home setting.*

A Dutch hospital currently uses a so-called 'smart patch' to remotely monitor COVID-19 patients, both on the general ward and at home after hospital discharge. This wireless sensor system measures heart rate, respiratory rate, temperature and activity and automatically predicts which patients deteriorate. Patients are now discharged home earlier while using this safety net.

Measurements of patients who are being monitored with this sensor system on a hospital ward or at home are sent to a medical observation center located within the hospital. At this place, all incoming patient data is automatically analyzed and checked by trained nurses. Machine learning methods are applied on the large data sets to accurately predict patient deterioration events. The nurse on the ward receives a notification on their smartphone, if measurements of ward patients deviate. As soon as patients are sent home, the nurse of the remote medical observation center keeps a watchful eye on these patients 24/7. He or she contacts the patient or his relative if worrisome signals are received. If necessary, a care professional will be sent directly to the patient's home to assess the situation.

Remote monitoring is beneficial for both patients and the hospital. The patient can be sent home earlier to recover in their own trusted environment. This modified care pathway contributes to safeguarding the scarce care capacity and to control the ever increasing healthcare costs. The hospital currently expands this innovation to other patient populations.

Exploring a safer care pathway from ICU to Home

To start exploring a safer care pathway from ICU to home with remote monitoring technology, one first needs to understand the possibilities, usability and reliability of wearable vital signs monitoring devices. In addition, the implications of implementing new technology from a clinician's and patient's perspective need to be understood, including the consequences for workflow processes within and outside hospital premises. Hereafter, an overview of the main findings and lessons learned during the work on this thesis are discussed (paragraph 9.1). It is followed by a description of the hurdles to overcome before implementation of this technology can become common clinical practice (paragraph 9.2). Paragraph 9.3 describes the different hospital-to-home models of care and the infrastructure needed to implement reliable remote home monitoring. Paragraph 9.4 summarizes lessons learned during the COVID-19 crisis and it is followed by recommendations for successful deployment of remote patient monitoring from hospital to home in paragraph 9.5. The discussion finishes with future perspectives of hospital to home care in 2030.

9.1 Main findings of this thesis

A. Reliability of wireless sensor systems

The first commercially available wearable medical devices for remote vital signs monitoring (such as heart rate, respiratory rate and temperature) appeared around 2011. Since then the market has been flooded with a variety of wireless sensors, most with unknown validity. The expectations and promises of those sensors to measure patient deterioration are enormous, although real world evidence on the reliability and usability, let alone effects on clinical outcome is lacking. Therefore we started with the validation of some of the wireless sensors in a clinical setting and asked ourselves: are current wireless sensors accurate enough to measure heart rate and respiratory rate in high-risk patients and can these sensors serve as a safety monitor in day to day care? The two wireless patch sensors that we clinically validated both measure the patient's electrocardiogram (ECG) signal and showed high accuracy for heart rate (Chapter 2 and 3). Such ECG-based wireless sensors often outperformed the current wired Intensive Care Unit (ICU) monitoring systems during periods of patient movement. This finding was also observed in Chapter 5 during validation of four new prototype sensors for wireless vital signs monitoring in volunteers. While ECG-based wireless sensors produce accurate heart rate readings, ECG appears to be a more vulnerable method to derive respiratory rate. Especially during periods of atrial fibrillation,

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respiratory rate from one of the wireless patch sensors (that uses mainly ECG characteristics to derive respiration rate) was too high. To improve the accuracy of respiration rate measurements, wireless sensor systems could benefit from combining multiple signal sources (e.g., ballistocardiography, ECG, impedance pneumography) to calculate respiratory rate, instead of deriving respiratory rate solely from a single source signal. Thus, the reliability of these first generation wireless sensors appears promising, but must still be considered in the early stages of development.

B. What is the effect of filtering artifacts

Vital signs are notoriously difficult to measure during patient movement because motion always generates signal artifacts. This is even more difficult in patients discharged from the ICU to the general ward or at home where patients are freely moving and no longer bedridden. The challenge for manufacturers of these wireless sensor systems - that will be used in ambulatory patients - is to effectively deal with the many artifacts. Filtering is often used to eliminate such disturbances in order to improve the reliability of the sensor system and prevent excessive false alarms (Chapter 2 and 3). A drawback of heavy filtering is that it reduces the ability to detect sudden changes in vital signs (e.g., cardiac arrest). However, we need to understand that these wireless sensors are intended to identify abnormal vital signs trends in unsupervised patients at a low-care setting, as opposed to the ICU setting, where 1:1 nursing is continuously available. In order to make the right decision which sensor is appropriate for use in certain clinical settings, it is important to realize that different methods used for artifact filtering will influence the capability to detect minor or major adverse events.

C. Can wireless sensors be used to make correct treatment decisions?

Before a physician is taking any 'life-or-death decisions', he or she needs to trust that the wireless sensor used is not underperforming compared to the routine system used. In Chapter 3, we used Clarke Error Grid analysis, a tool to evaluate the potential consequences of incorrect treatment decisions triggered by inaccurate wireless sensor measurements. Suppose, for example, that a patient on the ward develops opioid-induced respiratory depression with a dangerously low breathing rate (less than 6 breaths/min), while the wireless sensor reports a normal breathing rate (12 breaths/min). In this case, a doctor is unlikely to start any treatment, while discontinuation of the opioid and perhaps treatment with naloxone should be initiated quickly to reverse the respiratory depression. If not treated timely, this patient will deteriorate further and may be found unresponsive or even dead in bed. Therefore, wireless sensor systems need to

demonstrate that their vital sign measurements neither lead to unnecessary treatment nor to potentially dangerous failure to detect such events. Furthermore, the ability to detect events by tracking *changes in vital signs over time* and to obtain much more frequent vital signs measurements than a busy nurse can provide are important features of wireless sensor systems. We performed a descriptive analysis in Chapter 4 to evaluate this capability and found that the wireless sensors studied are able to detect abnormalities in vital signs trend patterns before adverse events were diagnosed. We also observed periods of tachycardia and tachypnea in patients without adverse events, but these changes occurred less frequently and were often transient or brief in duration compared to episodes in patients with adverse events.

D. Is the data transmission sufficient?

When vital signs data from wearable sensors are to be wirelessly transmitted while enabling the patient to freely move around, it is essential that no important data are lost. During our research we realized that data transmission is an important part to evaluate, since transferring data can fail for many reasons, such as loss of connection due to exceeding the functional Bluetooth range or Wi-Fi connectivity problems. Data gaps come in different variations, which are important to take into account during patient monitoring. For instance, one single data gap of 2 h will make it more difficult to recognize signs of ongoing complications than multiple scattered data gaps of a few minutes each. Within the four wireless sensor systems studied in Chapter 3, we found that the majority of data gaps did not exceed 15 minutes, suggesting that abnormal trends in physiology will be captured accurately in hospitalized patients. It is probably much more difficult to maintain data continuity when patients are being monitored in their own home setting. In patients discharged home after esophagectomy who wore a wireless patch sensor at home, we observed some data gaps longer than 4 hours, from various causes (Chapter 7). To date, it is not known to what extent the duration of data gaps reduces the ability to capture clinical deterioration on time both in a hospital and home setting. Obviously, manufacturers should carefully consider data continuity in the design of their systems and carefully test the robustness of their data transmission. This is especially relevant when a patient is monitored in their own home environment where hospitals cannot control quality and bandwidth of network connections.

E. The feasibility of home monitoring use cases

Wireless sensors that transfer data in a near real-time fashion might be valuable for in-hospital use, but may cause problems when used remotely in a patient's

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home. Data loss may occur more frequently and the need to continuously monitor a patient by trained professionals could be labor intensive when compared to patients that intermittently measure vital signs. Both feasibility studies described in Chapter 6 and 7 therefore have a completely different design to remotely monitor surgical patients in their own home setting after hospital discharge. In Chapter 6, patients after carotid endarterectomy performed blood pressure measurements themselves twice daily at home and these measurements were visible for researchers via an online dashboard. In Chapter 7, vital signs of patients after esophagectomy were monitored with a wearable patch sensor in the first days after hospital discharge while the vital signs trends obtained were shared with the surgical team. In this group of patients, continuous vital sign trend patterns were acquired, but the patients had no access to this information. In contrast, patients after carotid endarterectomy (Chapter 6) were able to observe their own blood pressure values through a telemonitoring application on a tablet computer. Overall, remote home monitoring was well-perceived by both patient populations and reported satisfaction scores and usability rates were high (Chapter 6 and 7). However, in the patient group monitored at home after carotid endarterectomy, one patient experienced stress because he was observing his blood pressure and thought his values were higher than expected. As a result, he increased the frequency of blood pressure measurements and developed stress-related hypertension; he was readmitted to the hospital for safety reasons. This reminds us that awareness is needed for possible unintended consequences when patients are able to closely follow their measured vital signs. In addition, well-functioning technology is not the only important part of a successful remote patient monitoring system. It should also incentivize patient-technology interactions that results in appropriate patient behavior. Interestingly, the majority of patients in the other study group (Chapter 7) reported that they did not mind the absence of any vital signs data on the mobile phone. At this point, we do not know the best way or to what extent certain information should be shared (or not) with patients being remotely monitored at home. In any case it seems likely that structured communication moments by phone or video between patients and care professionals on top of remote vital signs monitoring functionality, contribute to a more reassured feeling of patients (Chapter 7). This is also supported by our findings in Chapter 8 since patients and nurses during focus group meetings emphasized the importance of direct contact with a caregiver to successfully implement home monitoring technology.

F. The need for development of an integrated monitoring solution

At present, the various systems available to monitor a patient's condition on the ward and at home are not integrated in the hospital Electronic Medical Record (EMR), but organized in different silos. An integrated solution for remote patient monitoring on the ward and at home that automates the essential job of keeping watch on patients and can raise an alarm when a patient needs to be seen urgently is currently being developed in the collaborative EU-funded 'Nightingale' project (www.nightingale-h2020.eu). In Chapter 8 we identified the perceptions of stakeholders, such as patients, nurses and physicians, regarding the development and implementation of this integrated wireless patient monitoring solution. The main findings reflect once more that special attention is required to enable personal contact and communication with a patient on a hospital ward and at home if remote monitoring technology is to be deployed successfully.

9.2 Remote patient monitoring remains 'work in progress'

The newspaper article (see Box 1) and many similar to it create the impression that remote wireless patient monitoring with automated detection of patient deterioration is already in common use and implemented on a large scale. There is, however, considerable 'hype' surrounding wearable patient monitoring and a huge discrepancy between the amount of media attention for wearable technology and the number of hospitals that have actually implemented wireless patient monitoring. In addition, manufacturers of wireless patient monitoring technology often claim being able to accurately measure a wide range of vital signs to improve patient outcomes, while in reality the company is still little more than an idea and a website. We believe it is important not to believe the hype. There still is a lot of work to be done in this field and I will elaborate on a number of important aspects hereafter.

Validation in clinical practice

Many of the medical device companies have obtained a CE-mark or FDA approval to use wearable technology in clinical environments. Unfortunately, at present certification does not guarantee accuracy and reliability of wireless vital signs monitoring in patients at risk for clinical deterioration and is limited in making conclusions on usability, especially with vulnerable patients. Before meaningful implementation of wireless patient monitoring systems in daily clinical practice can succeed, it is crucial to rigorously test their performance and to validate the sensors in a true clinical setting [1]. Yet, in reality validation studies that critically

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test the reliability and accuracy of wearable sensors for continuous vital signs monitoring are often lacking.

There could be a number of reasons why well-performed validation studies are limited. First, there are only a few guidelines or consensus statements on how validation studies of wireless vital signs monitoring systems should be performed [2]. Secondly, for current regulatory approval under the European Medical Devices Directive, manufacturers only need to demonstrate that their device is capable of measuring the specified vital signs [3]. Moreover, many manufacturers' claims regarding accuracy cannot be cross-checked, since the results of such demonstrations are often not publicly available. Lastly, it is expensive and very time consuming to obtain ethical and regulatory approval for a validation study in real patients if a medical device does not yet have a CE-mark or FDA approval. As such, many manufacturers lack the know-how, as well as the incentive to execute proper validation studies. However, this situation is likely to change, since the new European Medical Devices Regulation (which takes effect on May 26, 2021) requires that *clinical* validation studies have been performed before certification can be provided. Consequently, when there is no demonstration that a new wireless wearable sensor can measure vital signs accurately in the abnormal physiology range, the new device cannot be used clinically. A proposed test protocol that highlights the strengths and weaknesses in terms of reliability and usability of (prototype) wireless wearable sensors is described in Chapter 5. This designed test protocol could be used by manufacturers of wireless wearable sensors to thoroughly test and improve their system before regulatory approval is requested. Examples of how one might perform a validation study in a clinical setting are shown in Chapter 2 and 3. Two important aspects of these chapters are highlighted below.

1. Comparison with routine monitoring standards

We used as reference standard our current ICU multiparameter monitoring system, but we soon realized that their accuracy levels - as indicated in the device specifications - were not achieved in practice. These specified accuracy limits are not obtained in real-life situations where patients are moving and talking, and were likely obtained in bench tests with patient simulator devices generating artificial vital signs waveforms. In such bench-tests the effects of changing electrode contact and patient movement are absent. Thus, there is a discrepancy between the accuracy specifications of ICU monitoring systems and their 'real world' performance. One possible explanation is disturbance of the signal due to pull on ECG electrode wires from patient movement and

malposition of the pulse oximeter probe that each reduce the reliability of the ECG or SpO2 signal. In practice, intensive care nurses 'filter' these artifacts when interpreting the patient's condition. Nonetheless, more than 85% of alarms in the Intensive Care Unit are false [4,5]. Therefore, we believe it is not reasonable to require from wireless sensors to perform within similar strict limits of agreement in clinical practice as compared to bench tests.

2. Trend monitoring versus real-time monitoring

It is important to understand the differences between monitoring at the ICU as opposed to monitoring at a general ward (or at home). For example, in the ICU an immediate response (within seconds) is warranted if a patient develops ventricular fibrillation. The combination of 1:1 nurse to patient ratio and real-time monitoring enables such a quick response. The current generation of wearable sensors is still far away from substituting ICU-grade monitoring systems, even though most sensors can measure vital signs in a near real-time fashion. For example, these wireless sensors may recognize a cardiac arrest, but as a result of artifact filtering the relevant alarm may be generated after several minutes rather than seconds. Continuously monitoring a patient's vital signs on a regular ward is preferred, but implementing a near real-time automated response to changes in vital signs will result in unacceptably high false alarm rates. This will lead to safety issues, since we cannot guarantee an immediate response with the current low nurse-to-patient ratio on the ward. Soon we realized that the reliability of wireless sensors should not rely solely on accurate single point estimates, but use the time series of continuously recorded vital signs to filter and obtain the most reliable estimate of vital signs over the last 10 to 30 minutes. We should therefore accept that expecting an immediate response to an acute event such as a cardiac arrest is not realistic with current wireless monitoring technology, but also realize that the likelihood of such events is much lower when no abnormal vital signs were present over the previous hours. Nevertheless, this monitoring strategy likely contributes much more to timely recognition of deterioration than the current standard of manual vital signs observations by the nurse three times a day [6,7]. Similarly, in patients discharged home after major surgery, measuring vital signs in a near real-time manner seems superfluous when patients are no longer at high risk for clinical deterioration. Besides this, a visit to assess a patient's condition at home cannot be executed immediately. Since clinical experience with remote monitoring on general wards or at home is still very limited, the optimal monitoring update frequency is yet unknown. In short, there is an unavoidable trade-off between the sensitivity to detect acute clinical deterioration events and an acceptable rate of false alarms which

still enables good working conditions for clinicians to use remote monitoring technology appropriately.

Introducing new technology on patients is a 'complex intervention'

Remote patient monitoring with wireless and wearable technology is new to nurses and clinicians working on a hospital ward and the introduction can be considered a 'complex intervention'. At the moment, remote monitoring technology is not part of routine care and not easy for a hospital to implement, especially not in a short timeframe. Care professionals are not used to work with wireless patient monitoring technology. They need to develop trust in such a new solution and their workflow needs to be adapted to successfully integrate the new sensor technology. I will now discuss each of those aspects.

Clinicians are not used to work with wireless sensors for vital signs monitoring

While in the early days, the old-fashioned 'bed chart' of pulse rate and temperature immediately showed whether a patient's condition was worsening or improving, intermittent nurse observations are nowadays hidden in the often complex and cumbersome electronic medical record (EMR). Many EMR clicks are needed to obtain a trend visualization of the collected vital signs, and often nurses do not have the time to create and interpret such overviews. As a result, interpreting vital signs *trends* disappeared from hospital ward nursing, while implementation of continuous vital signs monitoring on a regular ward means that nurses and physicians need to be able to interpret continuous vital signs trends. When discussing vital signs trend patterns of critically-ill patients for validation analysis with physicians and nurses (studies Chapter 2-4), we realized that care professionals on the general ward do not have this experience, as opposed to intensivists and anesthetists who are used to observing and acting upon changes in continuous vital signs data every day. Similar findings occurred when vital signs trends over 24 hours and over 7 days were shared with the surgical team in patients discharged home after esophagectomy (Chapter 7). For example, surgical team members would notice an overall high heart rate or transient very high respiratory rate in a patient recovering from major surgery and wonder whether this is normal or not. They then questioned whether it was acceptable to ignore these trends, since this would normally result in an increased Early Warning System (EWS) score indicating the need for more frequent patient observations. After a while, as physicians and nurses developed interpretation skills and were more used to observing the vital signs trends this anxiety disappeared. This shows that care professionals can rapidly learn how to deal with new information presented as time trends, but also that careful

preparation and time is needed to successfully implement a remote monitoring solution on the ward and in the home setting.

Trust in the wireless monitoring system

For a monitoring strategy to be effective, care professionals first need to trust the wireless monitoring system. Starting to use wireless monitoring technology on the ward does not mean that nurses will immediately respond as expected. For example, they may consider the system not accurate if the wireless sensor indicates a higher respiratory rate than their manually recorded observations. It has been well described that respiratory rate is often miscalculated or biased towards digit preferences [8-10]. Consequently, not all nurses will immediately embrace this new technology and some may continue to rely on their clinical routines and ignore the sensor information.

On the other hand, too much trust in the wireless monitoring system could be harmful as well, for example when nurses are too busy at night and decide to skip patient rounds, trusting the system to generate a warning signal if clinical deterioration occurs. It is known that a nurse's worry or 'sense of doom' often was present before abnormal vital signs were documented [11-13]. Therefore, it remains necessary for the nursing profession to use their clinical judgment skills while checking a patient's condition. A potential solution would be to make *structured nursing observations* obligatory and add this information (such as shortness of breath, clammy skin, confusion, 'nurse worry' [12]) to the automatically retrieved vital signs data to improve early recognition of patient deterioration (as explained in Chapter 8). Patients on the other hand, also need to trust they will be seen or contacted. Patients indicated that they perceive reduced personal contact as a potential risk when remote monitoring technology will be implemented on the ward and at home (Chapter 8). A well-balanced combination of automating vital signs monitoring with regular face-to-face contact moments between nurses and patients is therefore imperative to gain trust in the use of new remote monitoring technology. Finally, patients should have justifiable trust in the care team to accept the use of wireless monitoring technology.

Changes in the clinician's workflow

Another important aspect is the need to change a care professional's workflow for sustainable deployment of remote patient monitoring technology. It is thought that remotely monitoring a patient's vital signs will decrease nurses' workload which allows them to free up time for other activities [14,15]. To reach this condition, high usability of the system is key to care professionals. This

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includes fully integrated data flow from the wearable sensors to the hospital EMR and no requirement for the nurse to add data manually. However, most hospitals have not integrated data from remote monitoring systems into their EMR and connectivity is hampered by a lack of standardized interfaces. Consequently, nurses are still forced to enter automatically recorded vital signs manually into the EMR and therefore do not experience the full benefits of this innovation. This creates understandable resistance to workflow changes as part of a new care pathway. Again, implementing remote patient monitoring on a general hospital ward takes effort and time.

Hospitalized patients

Goal: early and safe discharge

- Continuous vital signs monitoring
- 24/7 supervision of medical call centre with video or phone support
- Quick response to patient deterioration events
- Home visits of clinicians
- First days after hospital discharge

1

Patients presenting to Emergency Department

Goal: not admitting patients to the hospital

- Continuous vital signs monitoring
- 24/7 supervision of medical call centre with video or phone support
- Quick response to patient deterioration events
- Home visits of clinicians
- First days after ED presentation

2

Hospitalized patients

Goal: safe discharge & preventing readmissions

- Daily spot checks of vital signs ('self-monitoring') with connected devices
- Daily supervision of medical call centre with video or phone support
- First days after hospital discharge

3

Patients with chronic conditions

Goal: reduce hospital admissions & outpatient visits

- Daily or weekly spot checks of vital signs and symptoms ('self-monitoring') with connected devices
- Daily or twice weekly supervision of nursing specialists with video or phone support
- Months to years

4

Figure 1. Four hospital-to-home care models

9.3 - Home monitoring: another 'complex' care model

To answer the question whether it is possible to implement a safer pathway from ICU to home with wireless and wearable technology, we first need to understand the current state regarding home monitoring. The promise of hospital-at-home solutions in the patient's own home setting is a reduction of hospital length

of stay (by safe early discharge), and perhaps preventing hospital admission in certain patient populations who may benefit from home treatment rather than admission (such as frail elderly patients). To date, hospital-level care at home for patients after major surgery or medical illness has not been widely deployed, and evidence on cost-effectiveness is scarce. A complete infrastructure with clinical and technical support needs to be set up and large investments are needed to effectuate the implementation of remote home monitoring.

I will discuss these aspects hereafter.

A variety of divergent models have been labelled as hospital to home care in the literature. This diversity causes debate about the definition of hospital to home care, as well as difficulties in its perceived effectiveness [16]. Four different hospital to home models are illustrated in Figure 1. Each of these four models represents different characteristics organized from highest hospital-level care at home (nr. 1) to the lowest hospital at home type of care (nr. 4). With both models nr. 1 and nr. 2, a quick response needs to be guaranteed if clinical deterioration events occur and as such a remote medical observation center with trained professionals should be available 24/7. With models nr. 3 and nr. 4, patients are self-monitoring their vital signs and symptoms a few times a day or week. Remote assistance is available on a daily basis, but not offered 24/7.

- In the context of this thesis, we define 'hospital to home' care as early and safe discharge of hospitalized patients with support of wireless and wearable monitoring technology at home (Model nr. 1). For example, patients after esophagectomy who are discharged home several days earlier than before. If the remote medical observation center detects signs of possible deterioration in a patient who was sent home early, staff will contact the patient (or relative) to verify any symptoms of concern. Depending on the severity of the patient's condition, a community nurse or the patient's general practitioner can visit the patient at home to assess the situation. In case of severe deterioration, the patient will be readmitted to the hospital. To date, such a hospital-to-home model is largely uncharted territory.
- Model nr. 2 includes patients presenting at the Emergency Department who are sent home and observed remotely (using wearable wireless monitoring equipment) [17]. Here there is reasonable doubt whether the patient really needs to be admitted. For example, an elderly patient with a primary diagnosis of a pneumonia who will be remotely monitored at home instead of admitted to a general care ward. Their condition is monitored by a remote medical observation center to enable the ability to respond quickly in case

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of impending clinical deterioration (similar to Model nr. 1). The hope is that avoiding hospitalization will prevent delirium and loss of functional status associated with hospitalization of frail elderly patients [18,19] .

- Model nr. 3 represents a 'hospital to home' care model without the need for continuous vital signs monitoring and an immediate care response. In this case, patients are asked to measure their own vital signs twice or three times daily with medical 'spot-check' devices connected to a telemonitoring platform. A medical call center checks the patient's condition on a daily basis, but does not offer 24/7 supervision. For example, a patient after carotid endarterectomy who self-monitors his blood pressure twice daily to check his recovery and to prevent hospital readmissions (as discussed in Chapter 6).

- Model nr. 4 represents a remote monitoring strategy which is increasingly being used to monitor patients with e.g., COPD, heart failure or hypertension at home for a prolonged period of time in order to reduce outpatient visits and rehospitalization [20]. Patients enter their blood pressure, weight or other symptoms into a telemonitoring application and if necessary, a video call could be initiated by a nursing specialist for example, to initiate or adapt treatment if needed.

Organization of care outside hospital premises

Implementing a hospital to home service such as Model nr. 1 (Figure 1) is difficult and time consuming and can therefore be considered a complex clinical care model [21]. Primarily, because hospitals now need to organize care outside their own hospital premises and also because responsibilities between care professionals inside and outside the hospital need to be redefined. Nurses taking care of patients on the ward believe that remote patient monitoring at home is not part of their job (Chapter 8). However, a remote medical observation center needs experienced individuals to remotely monitor a patient's condition at home and send support if vital signs derail and the patient does not feel well. If patients are being discharged home earlier with support of wireless monitoring technology, hospitals need to take a share in the responsibility to provide clinical assistance and technical support. This must be organized in collaboration with stakeholders within the community, such as general practitioners, community nurses and home care organizations. Such an infrastructure must be in place before the first patient can be remotely monitored at home, which represents a considerable barrier to adoption.

Financial barriers

Another possible reason for the lack of implementation of hospital-level care at home may be a reduced incentive for hospitals to adopt such models, since no payment structure exists to reimburse the full chain of remote home monitoring services. Although insurers in the Netherlands have recently reimbursed a few e-Health services, such as the provision of video consultations, most other payments to hospitals are only transferred if care occurred within hospital premises. This financial model hinders uptake of hospital-to-home care services in practice. Furthermore, upfront investments in sensor equipment and IT need to be made as well the personnel costs for setting up a remote observation center. This will only be financially viable if remote patient monitoring is performed at scale. If society desires to transfer more complex care from the hospital to the home setting, we will need to invest in the technology and collaboratively modify care pathways, before any long term benefits might be realized.

9.4 Lessons learned from COVID-19

Whereas the uptake of remote patient monitoring by hospitals was progressing at a snail's pace over the past years, the COVID-19 pandemic has accelerated the adoption of digital innovation. A surge of critically ill patients at risk for rapid deterioration led to a large number of COVID-19 related hospital admissions over a two-month period (March-April 2020). Since scarce ICU beds quickly became occupied, while most patients required close monitoring, hospitals instantly had to anticipate and reorganize their care pathways. Rapid deployment of remote patient monitoring applications on the hospital ward and at home became an extremely valuable and necessary solution to support clinicians and a way to cope with demand for expanding capacity issues.

Rapid implementation of continuous monitoring on the COVID-19 cohort ward

University Medical Centre Utrecht had to manage many more acutely ill patients on the ward than usual, with the majority requiring high levels of oxygen support. Nurses reported frightening experiences of dealing with patients that showed unexpected and sudden respiratory decline [22,23] with deep oxygen desaturation. In addition, new patients were isolated to prevent further transmission of the virus. Consequently, nurses could not easily check upon the patient's condition. Therefore, the hospital decided to quickly implement continuous vital signs monitoring on the COVID-19 cohort ward to improve detection of patients at risk for respiratory failure and to limit the frequency and exposure of hospital staff to be in close proximity of COVID-19 patients.

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Lessons learned

Several remote monitoring projects were conducted in our hospital in the past several years. Armed with that experience, we were quickly able to effectively organize and implement remote patient monitoring technology during the COVID-19 crisis. A roll-out process that typically requires months of preparations was now executed in days. This is quite a challenge considering the fact that new sensor technology was introduced to the workflow process of nurses in a very short timeframe. The technical implementation, however, is only a minor part of all the work that needs to be done to deploy wireless vital signs monitoring on the ward. During the implementation period, I once more realized that paying attention to nurses and the nursing profession is key for a successful implementation. We spoke with dozens of nurses throughout the implementation process, listened to their ideas and concerns, and evaluated the use of this new monitoring technology day by day. This contributed much to the smooth implementation of wireless monitoring technology on the ward. These experiences teach us two things:

1. it pays off to invest upfront in the full 'hospital to home' infrastructure for remote patient monitoring before longer term benefits can be realized, and
2. sustained attention for the needs and feedback from every nurse and doctor working on the ward adopting remote monitoring technology is the invisible gold for a successful implementation strategy.

9.5 Recommendations for successful deployment of remote patient monitoring from hospital to home

Based on our experiences with validation studies and initial implementation of wireless patient monitoring technology both in hospital and at home, we suggest the following recommendations for a successful and sustainable deployment of remote patient monitoring.

Start small and become acquainted with remote patient monitoring

Hospitals should not wait until wireless patient monitoring on hospital wards and at home in the first days after discharge becomes common practice. They should start exploring its application together with clinicians and patients and gather experience with solutions on a small scale even though current technology may not yet be as advanced or reliable as desired. This requires sufficient funding from hospital boards to experiment with wireless monitoring technology. Once

hospitals commit to investing in this technology, they should choose systems that can demonstrate that they integrate well with the hospital's EMR. This avoids that caregivers must work with multiple 'standalone' systems and duplicate data entry. Lastly, hospitals need to prepare their organization to collaboratively work with stakeholders in the region, such as general practitioners and community nurses to allow smooth implementation of hospital to home practices.

Involve stakeholders from the very beginning

The hospital board should make the importance of organizing remote patient monitoring from hospital to home explicit. To support this message, they should try to reach the care professionals on the shop floor. This can be organized by hospital management to appoint someone (an 'idea champion') who realizes a feedback loop within the organization to learn from experiences of other stakeholders with regard to remote patient monitoring [24]. Another important prerequisite is to involve stakeholders from the very beginning, paying attention to the clinicians' needs and ensure that the board's promises are kept. For example, with regards to wireless vital signs monitoring on the hospital wards, substantial effort must be put into integration of data from wireless monitoring solutions into the hospital EMR to reduce nurses' workload of having to enter vital signs manually each time. If such preparations are not initiated, nurses will rapidly lose their positive attitude and willingness to use the system.

Organize the escalation of care response in the home setting

Within the hospital, the escalation pathway for patient deterioration is now widely known. If a nurse notices that her patient's condition is worsening, a Rapid Response Team (RRT) is summoned to the bedside to assess and treat the patient to prevent further clinical deterioration [25,26]. A similar escalation of care that triggers the right response in patients being remotely monitored at home is currently missing. However, it is necessary to design that escalation pathway before the first patient is discharged home with remote monitoring. To facilitate this response pathway, designing the organization of a remote medical observation center staffed with experienced medical professionals that observe patients remotely at home is necessary. In addition, a clear delineation of responsibilities between the various professionals, including the role of general practitioners must be defined, such as criteria for deciding which patients can safely recover in their home setting, and how to decide when remote monitoring can be discontinued.

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Incorporate personal contact moments as integral part of remote patient monitoring

Special attention is required to guarantee that personal contact and communication is not lost when a patient is being remotely monitored at home. Introducing new technology that enables monitoring of a patient's condition at a distance comes at a risk of inadvertently reducing patient contact. Patients may become stressed or anxious if they feel questions remain unanswered or if they worry about their condition. Hospitals should prevent these situations by scheduling contact moments (via phone or video) between patients and care professionals. This is especially relevant in the early days after hospital discharge.

If all these conditions are created, Maria Boerhaave's hospital - as mentioned at the beginning of this chapter - will be well prepared to successfully implement a safer care pathway from hospital to home with wireless monitoring technology. Nevertheless, do not believe the 'hype' that this is all very simple and already available, but start to gain experience with this innovative approach in your own hospital.

9.6 A glimpse of the future: remote patient monitoring in 2030

By 2030, the academic hospital formerly led by Maria Boerhaave, followed the advice and recommendations she received from the technical physician back in 2020. This hospital has learnt how to successfully implement wireless patient monitoring on their hospital wards. It is now even common practice among the majority of hospitals in the Netherlands. Hospitals have intensified collaborations with medical device manufacturers and digital health companies. This has resulted in miniaturized wireless monitoring systems that also provide reliable blood pressure measurements and oxygen saturation readings over time without the necessity to change batteries each day. There are well-developed standardized test protocols for evaluating new medical devices in clinical practice, which have been applied regularly. At least half of the hospitals have integrated data from validated wireless sensors into their EMR, and the first large clinical trials have demonstrated that these systems improve patient safety, can safely reduce hospital length of stay and readmission rates, while at the same time reducing nurses' workload.

Also, the first Artificial Intelligence (AI) models have been validated and successfully used in clinical practice to early predict clinical deterioration in hospitalized patients and for patients discharged home. These models were built in collaboration between academia and industry and with support from the European Commission that funded the infrastructure for a publicly accessible

open-source database containing thousands of de-identified, well annotated real-time patient data.

The major European hospitals have now substituted approximately 20% of hospital-level care to the patient's home setting. This movement accelerated considerably once the first remote medical observation centers were set up and staffed with trained medical professionals who safeguard 24/7 supervision of patients monitored in their own home setting. To keep healthcare finances under control, smaller hospitals have subcontracted services from these remote medical observation centers to provide remote supervision of their patients discharged home.

Success stories show that a smooth integration of the remote monitoring equipment turned out to be only a minor part of the implementation process. Pro-active communication and regular planned personal contact moments between patients (and their relatives) and clinicians via video consultations proved to be the actual key to successful implementation of hospital-to-home services. This is how hospitals deliver truly patient-centered care in 2030.

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APPENDICES

Summary

Nederlandse samenvatting

List of publications

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About the author

Summary

When patients leave the Intensive Care Unit, they usually transition from a setting with a high nurse to patient ratio where they are closely monitored to a general ward where nurses have to deal with large numbers of patients and often check a patient's vital signs not more than once every 4-8 hours. Early signs of patient deterioration may therefore be easily overlooked. In patients discharged home, vital signs are no longer monitored at all, while hospital length of stay is much shorter than previously. In the past several years, several wearable and wireless sensors for remote vital signs monitoring came available on the market which could capture patient deterioration at an earlier stage. Research in this field is largely uncharted territory. In this thesis, the performance and clinical utility of wireless and wearable sensors for vital signs monitoring is studied both in the hospital and home setting.

Part I investigates the measurement performance of wearable and wireless vital signs sensors to detect patient deterioration. A number of wearable sensors have obtained approval for medical use, but evidence on reliability and usability in clinical practice is lacking. **Chapter 2** investigates whether a wireless patch sensor placed on the chest is able to reliably measure heart rate and respiratory rate continuously in high-risk surgical patients. In an observational methods comparisons study, patients were measured with both the wireless sensor and an intensive care unit-grade monitoring system. Bias and 95% limits of agreement for heart rate were -1.1 (-8.8 to 6.5) beats per minute, which means that the wireless is capable to accurately measure heart rate. The accuracy of respiratory rate was outside acceptable limits with a bias of −2.3 breaths per minute and wide limits of agreement (−15.8 to 11.2) breaths per minute. Filtering over 15 min data effectively eliminates artefacts (from movements or talking) and hence improves accuracy. Measuring respiration rate needs further optimization to reduce the incidence of false alarms and allow timely recognition of altered breathing patterns. It is unknown how performance of wireless monitoring systems with different sensing principles differ and how well they perform against a typical intensive care unit-grade patient monitor. In **Chapter 3**, we therefore determined whether two wireless patch sensors (both placed on the chest), a bed-based mattress sensor and a patient-worn monitor can reliably measure heart rate and respiratory rate continuously in high-risk surgical patients admitted to a step-down unit. All sensors were highly accurate for heart rate. Respiratory rate is clearly harder to measure.

Three of the four sensors were reasonably accurate for measuring respiratory rate with a bias not greater than 0.8 breaths per minute when compared with the intensive-care monitor. One of the wireless patch sensors (similar to chapter 2) clearly overestimated respiratory rate, with a bias of 4.4 (limits: −4.4 to 13.3) breaths per minute. However, the tested devices were accurate enough to identify abnormal patterns in respiratory rate. Trend monitoring with wireless and wearable sensors could therefore be valuable to timely detect patient deterioration. In **Chapter 4**, the same wireless and wearable sensors of Chapter 3 were used to describe their ability to detect adverse events in high-risk patients. A descriptive analysis was performed of all vital signs trend data obtained in high-risk surgical patients during the initial days of recovery at a step-down unit and subsequent surgical ward. Twenty adverse events occurred in 11 of the 31 patients included of which atrial fibrillation (AF) was most common (20%). The onset of AF was recognizable as a sudden increase in heart rate in all recordings, and all patients with new-onset AF after esophagectomy developed other postoperative complications. Patients who developed respiratory insufficiency showed an increase in respiratory rate and a decrease in oxygen saturation (SpO_2) but an increase in heart rate was not always visible. In patients without adverse events, temporary periods of high heart rate and respiratory rate are observed as well, but these were transient and less frequent. Current systems for remote wireless patient monitoring on the ward are capable of detecting abnormalities in vital sign patterns in patients who develop adverse events. In **Chapter 5** a 90-min test protocol was designed and applied to assess the validity, reliability and usability of new wearable wireless sensors for continuous vital signs monitoring. We illustrated how the protocol might be used by evaluating the performance of four prototype wearable, wireless, multi-parameters sensors during a method comparison study under 'laboratory' conditions and subsequently during five days of 'field-testing' at home in twenty volunteers. Testing of agreement and concordance of heart rate, respiratory rate, non-invasive blood pressure and skin-temperature of the prototype sensors versus reference standards showed considerable variation across devices. High percentages of data loss (>35%) for two devices were seen. The mean system usability score varied from low usability to 'ok' usability. The designed 90 min test protocol with 5-day of field-testing is suitable to promptly highlight several strengths and weaknesses of (prototype) wireless wearable sensors for remote vital signs monitoring.

Part II addresses the potential of remote home monitoring in patients recovering after surgery. Chapters 6 and 7 have a completely different design

to remotely monitor surgical patients in their own home setting. In **Chapter 6**, the feasibility of daily blood pressure self-measurements at home following carotid endarterectomy was studied as well as patient experiences. Thirty patients measured blood pressure at home twice daily for 30 days with an ambulatory blood-pressure monitor. All measurements were daily checked via an online telemonitoring application. Post-discharge, four patients experienced an adverse event of which two were hemodynamic in origin: readmission due to stress-related hypertension and postoperative bleeding requiring surgery. Over 90% of patients experienced home blood-pressure monitoring as positive and all except one recommended adding home blood-pressure monitoring to standard care. Postoperative 'self-measurements of blood-pressure after hospital discharge was feasible and well accepted in patients after carotid endarterectomy. Future studies need to address the potential clinical gain of remote blood-pressure monitoring in early detection and management of patients at risk for postoperative hemodynamic complications. **Chapter 7** assesses the technical feasibility and experiences of patients discharged home early after esophagectomy while being remotely monitored with a wireless patch sensor. In an observational feasibility study, vital signs (heart rate, respiratory rate, skin temperature and steps) of patients were monitored with a wearable patch sensor during the first seven days at home after discharge. Vital signs trends were shared with the surgical team once a day and they were asked to check the patient's condition by phone each morning. Patients appreciated that surgeons checked their vital signs daily and were happy to be called by the surgical team each day. Overall data loss of vital signs measurements at home was 25%; both data loss and gap duration varied considerably among patients. Remote monitoring of vital signs combined with telephone support from the surgical team was feasible and well perceived by all patients. However, minimal requirements regarding optimal measurement frequency and data continuity for adequate home monitoring need to be investigated in more detail. Future studies need to evaluate the impact of home monitoring (both self-measurement as well as continuous monitoring) approaches on patient outcome as well as cost-effectiveness.

An organizational perspective on remote patient monitoring from hospital to home is outlined in **Part III** of this thesis. **Chapter 8** conducts a methodological approach to include stakeholder perceptions in the design of wireless patient monitoring solutions. This study aimed to elicit the values and perspectives of key stakeholders on the potential utility and risks of wireless patient monitoring in the hospital and at home to guide important design choices during the development

of such systems. A theoretically grounded approach: 'value sensitive design' was selected to conduct this analysis. Four focus group meetings with nurses, patients, relatives and junior doctors were conducted. Six topics were discussed most often regarding usability, alarm strategy, clinical judgment, personal contact, reassurance and reliability. Communication and personal contact between health professionals and patients or relatives and sophisticated alarm notification systems were found to be key design options to ensure successful implementation of remote monitoring. Incorporating stakeholder perceptions within a value sensitive design approach is essential to anticipate on potential problems and to enable early formulation of design options that will facilitate the development and future uptake of systems for wireless patient monitoring. In **Chapter 9**, a thorough discussion is described about lessons learned and future directions for remote patient monitoring from hospital to home.

NEDERLANSE SAMENVATTING

Patiënten herstellende van een grote operatie lopen het risico op het ontwikkelen van postoperatieve complicaties. Voordat zich levensbedreigende complicaties voordoen, zijn vaak al uren voorafgaand symptomen van achteruitgang, zoals een verandering in de ademhaling of hartslag van de patiënt aanwezig. Nog te vaak worden deze vroege signalen niet of te laat herkend. Een van de problemen is het feit dat de vitale functies van patiënten op een verpleegafdeling meestal niet vaker dan eens per 4-8 uur gecontroleerd worden. Bij patiënten die met ontslag naar huis gaan, worden vitale functies helemaal niet meer gemeten, terwijl de opnameduur tegenwoordig veelal korter is dan ooit tevoren. In de afgelopen jaren zijn verschillende draagbare en draadloze sensoren op de markt gekomen voor monitoring van vitale functies op afstand. Deze sensoren kunnen mogelijk achteruitgang van de patiënt eerder detecteren. Onderzoek op dit gebied is nieuw en grotendeels onbekend terrein. Derhalve besteedt dit proefschrift aandacht aan de klinische inzetbaarheid van deze *wearables* voor monitoring van vitale functies zowel in het ziekenhuis als thuis.

Deel 1 van dit proefschrift richt zich op de performance van draagbare en draadloze sensoren voor het meten van vitale functies om achteruitgang bij patiënten te detecteren. Ondanks het feit dat deze draagbare sensoren zijn goedgekeurd volgens de richtlijn medische hulpmiddelen, ontbreekt veelal het bewijs over betrouwbaarheid en gebruiksgemak van deze toepassing in de klinische praktijk. In **Hoofdstuk** 2 wordt onderzocht of een nieuwe draadloze sensor die op de borst wordt geplakt ('een slimme pleister') in staat is om betrouwbaar de hartslag en ademhalingsfrequentie te meten. In een 'method comparison' studie wordt deze sensor vergeleken met een referentie methode, in dit geval een intensive care monitor. Het gemiddelde verschil tussen de twee methoden was slechts -1.1 hartslagen per minuut, waarbij 95% van de metingen -8.8 tot +6.5 hartslagen per minuut verwijderd zijn van de referentie meting. Dit betekent dat de draadloze sensor in staat is om accuraat de hartslag te meten. De nauwkeurigheid van de ademhalingsfrequentie presteerde niet binnen acceptabele grenzen, met een gemiddeld verschil van 2.3 ademteugen per minuut met wijde 95%-grenzen van -15.8 tot 11.2 teugen per minuut. De accuraatheid verbetert sterk nadat artefacten in de data zijn geëlimineerd door filtering toe te passen over perioden van 15 minuten. Het meten van de ademhalingsfrequentie moet verder geoptimaliseerd worden om de incidentie op valse alarmen te reduceren om zo tijdig veranderde ademhalingspatronen

te kunnen herkennen. In **Hoofdstuk 3** wordt onderzocht wat de performance is van draadloze monitoring systemen ten opzichte van elkaar en hoe nauwkeurig deze zijn wanneer de meetwaarden worden vergeleken met een intensive care monitor. Hiervoor worden twee draadloze 'pleister' sensoren (beiden op de borst geplakt) gebruikt, een contactloze bedsensor (onder het matras) en een draagbare patiënten-monitor (om de bovenarm) bij patiënten opgenomen op de Medium Care na chirurgie. Al deze sensoren zijn accuraat in het continu meten van de hartslag. Het nauwkeurig meten van de ademhalingsfrequentie is duidelijk wat moeilijker. Drie van de vier sensoren bleken overwegend accuraat te zijn met een gemiddeld verschil niet groter dan 0.8 ademteugen per minuut ten opzichte van de intensive care monitor. Eén van de twee draadloze 'pleister' sensoren (dezelfde als hoofdstuk 2) was beduidend minder nauwkeurig en overschatte de ademhalingsfrequentie met een gemiddeld verschil van 4.4 ademteugen per minuut. Echter, al deze sensoren zijn wel in staat om veranderende ademhalingspatronen te detecteren. Trend monitoring met behulp van draadloze en draagbare sensoren kan daarom waardevol zijn in het tijdig detecteren van achteruitgang bij patiënten. In **Hoofdstuk 4** zijn dezelfde draadloze en draagbare sensoren gebruikt als in Hoofdstuk 3 om te beschrijven in hoeverre deze in staat zijn om complicaties ('adverse events') te detecteren. Een beschrijvende analyse is uitgevoerd van alle trends in vitale functies verkregen bij hoog-risico patiënten tijdens de eerste dagen na chirurgie op de Medium Care en verpleegafdeling. Twintig 'adverse events' traden op in 11 van de 31 geïncludeerde patiënten, waarvan atrium fibrilleren (AF) het vaakst (20%) voorkwam. Het begin van AF was te herkennen als een plotselinge stijging in hartslag bij alle metingen. Alle patiënten waarbij AF de novo vastgesteld was na een oesofagusresectie ontwikkelden ook andere postoperatieve complicaties. Patiënten die een respiratoire insufficiëntie ontwikkelden lieten een stijging in de ademhalingsfrequentie en een daling in zuurstofsaturatie (SpO_2) zien, maar een stijging in de hartslag was niet altijd aanwezig. In patiënten zonder 'adverse events' werden ook tijdelijke perioden van een hoge hartslag of ademhalingsfrequentie geobserveerd, maar deze veranderingen waren kortstondig en minder frequent. Deze studie laat zien dat de huidige draadloze systemen voor het op afstand monitoren van patiënten op de verpleegafdeling in staat zijn om afwijkingen te detecteren in de patronen van vitale functies bij patiënten die complicaties ontwikkelen. In **Hoofdstuk 5** is een 90-minuten durend test protocol ontworpen en toegepast om de validiteit, betrouwbaarheid en gebruiksgemak te bepalen van nieuwe draagbare en draadloze sensoren voor het continu monitoren van vitale functies. Het wordt geïllustreerd hoe dit protocol gebruikt kan worden door de performance van vier prototype draagbare en draadloze sensor systemen te

evalueren in een laboratorium setting en vervolgens tijdens een vijfdaagse test thuis bij 20 vrijwilligers. Het testen van de betrouwbaarheid van deze prototype sensoren voor hartslag, ademhalingsfrequentie, niet-invasieve bloeddruk en huidtemperatuur t.o.v. de referentie standaard liet aanzienlijke verschillen zien tussen de sensor systemen. De hoeveelheid data verlies van twee van deze sensor systemen was hoog (>35%). Het gemiddelde gebruiksgemak varieerde op een 'gebruiksvriendelijkheid' schaal van laag naar goed. Met een dergelijk test protocol kunnen snel de verschillende sterke en zwakke punten van (prototype) draadloze en draagbare sensor systemen voor het op afstand monitoren van vitale functies bloot worden gelegd.

Deel 2 richt zich op de haalbaarheid van het op afstand monitoren van patiënten thuis na chirurgie. Hoofdstukken 6 en 7 hebben een totaal verschillende aanpak om op afstand patiënten te monitoren in de eigen thuisomgeving. Om inzicht te krijgen in het postoperatieve bloeddrukbeloop na een carotis endarteriëctomie na ontslag en de postoperatieve zorg uit te breiden naar de thuisomgeving, wordt in **Hoofdstuk 6** de haalbaarheid onderzocht van het tweemaal daags thuis de bloeddruk meten door de patiënt zelf tijdens de eerste 30 dagen na ontslag. De meetwaarden werden dagelijks op afstand gecontroleerd via een online telemonitoring platform. Deze studie laat zien dat 'zelfmeting' van de bloeddruk thuis na ontslag uit het ziekenhuis goed wordt geaccepteerd en zelfs wordt aanbevolen door patiënten. Toekomstige studies moeten laten zien wat de baten zijn van het monitoren van de bloeddruk van patiënten op afstand en in hoeverre de postoperatieve zorg naar thuis kan worden uitgebreid om detectie en behandeling van patiënten met een verhoogd risico op postoperatieve hemodynamische complicaties mogelijk te maken. In **Hoofdstuk 7** worden de technische haalbaarheid en ervaringen onderzocht van het op afstand thuis monitoren van trends van vitale functies bij patiënten na een oesofagusresectie. De parameters (hartslag, ademhalingsfrequentie, huidtemperatuur en stappen) van de patiënt werden gedurende 7 dagen na ontslag continu geregistreerd via een draadloze sensor op de borst. Eenmaal per dag werden deze trends van vitale functies gedeeld met het chirurgische team om dit te beoordelen waarna de patiënt werd gebeld om zijn of haar conditie te kunnen checken. Patiënten waardeerden het feit dat het chirurgische team dagelijks hun vitale functies beoordeelden en ze vonden het erg prettig dat ze dagelijks werden gebeld door hen. Het gemiddelde dataverlies thuis was 25%, en zowel de hoeveelheid dataverlies als ook de duur van de data gaten varieerde behoorlijk tussen patiënten. Deze studie toont aan dat het op afstand monitoren van trends van vitale functies gecombineerd met telefonisch contact haalbaar is en

goed wordt geaccepteerd door patiënten. Toekomstige studies moeten laten zien wat de impact is van thuismonitoring van chirurgische patiënten (zowel via 'zelfmetingen' als continue telemonitoring) op het gebied van patiënten uitkomsten en kosten-effectiviteit.

In **Deel 3** wordt er een organisatie perspectief geschetst voor de inzet voor monitoring van patiënten op afstand van ziekenhuis naar huis. In **Hoofdstuk 8** wordt een methodologische aanpak beschreven om de waarden en perspectieven van key stakeholders ten aanzien van het potentiele gebruik en de risico's van draadloze monitoring van patiënten op afstand in het ziekenhuis en huis uit te vragen, om belangrijke 'design' keuzes tijdens de ontwikkeling van dergelijke systemen te sturen. De gefundeerde theorie die hiervoor is ingezet wordt 'value sensitive design' genoemd. De onderwerpen die het meest bediscussieerd zijn tijdens de vier focusgroepen met verpleegkundigen, patiënten, mantelzorgers en zaalartsen waren gebruiksgemak, alarm strategie, de 'klinische blik', persoonlijk contact, geruststelling en betrouwbaarheid. Communicatie en persoonlijk contact tussen zorgprofessionals en patiënten of mantelzorgers en een geavanceerd alarm notificatie systeem bleken de meest essentiële 'key design' opties om de kans te vergroten op succesvolle implementatie van monitoring op afstand. Het incorporeren van stakeholder percepties binnen een 'value sensitive design' aanpak is essentieel om tijdig te anticiperen op potentiële problemen en om in staat gesteld te worden vroegtijdig 'key design' opties te formuleren die de ontwikkeling en toekomstige ingebruikname van dergelijke systemen voor draadloze patiënten monitoring faciliteren. Overdenkingen op basis van de studies in dit proefschrift, geleerde lessen uit de praktijk, en suggesties voor toekomstige ontwikkelingen worden uitgebreid bediscussieerd in **Hoofdstuk 9**. Tevens wordt er een kijkje gegeven in de benodigde organisatie om monitoring van patiënten op afstand (een 'complexe interventie') zowel in het ziekenhuis als thuis mogelijk te maken.

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* contributed equally

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About the Author

Martine Josefien Maria Breteler was born on 31th of May 1989 in Almelo, the Netherlands. She grew up with her parents, brother and sister in Bornerbroek. After finishing her secondary school at Pius X College Almelo in 2007, she started with her Bachelor Technical Medicine at the University of Twente, Enschede. In 2010, she continued with the 3-years master program 'Medical Signaling' of Technical Medicine. To broaden her knowledge and interest in the field of health services and management, she obtained a master's degree in Health Sciences (cum laude) in 2012. Thereafter, she pursued her Technical Medicine clinical internships at the Department of Intensive Care at the Radboud University Medical Center (UMC), the Department of Clinical Neurophysiology at Medisch Spectrum Twente Enschede, the Neurology Department of Yale University School of Medicine, Connecticut, USA and at the Anesthesiology Department of UMC Utrecht. She graduated in 2014 with her master thesis at the Intensive Care and Clinical Neurophysiology department of Medisch Spectrum Twente Enschede in collaboration with Philips Healthcare which was focused on continuous EEG monitoring for delirium detection at the ICU.

Thereafter, she started with her job as product researcher at FocusCura, a healthcare innovation company that is developing e-health solutions to help elderly and chronically ill stay independent. She was determined to pursue an academic career and got the opportunity from prof. dr. ir. Daan Dohmen to collaborate with prof. dr. Cor Kalkman to work on a PhD project plan 'A Safer Care Pathway from ICU to Home'. The title has not changed ever since. In 2016, prof. dr. Cor Kalkman has been awarded a grant by the Horizon 2020 program of the European Commission called 'NIGHTINGALE', to develop a wearable system for wireless intelligent monitoring of high risk patients both in hospital and at home together with the MedTech industry. Thereafter, Martine was able to start working as the Nightingale clinical validation lead and as a PhD candidate under supervision of prof. dr Cor Kalkman, prof. dr. ir. Daan Dohmen and dr. Taco Blokhuis. She received an e-Health grant from the ZonMw Citrienfonds program

for her 'Wireless Vitals' project. During her PhD career she also supervised research projects of over 15 master's students. She combined her PhD with working for FocusCura and later on Luscii, a health IT company that develops home monitoring services for patients and healthcare professionals.

In November 2020, she started with a full-time position as a Technical Physician project lead at UMC Utrecht. In her new role, she continues with her passion to further develop, implement and study remote monitoring projects both within hospital and home.