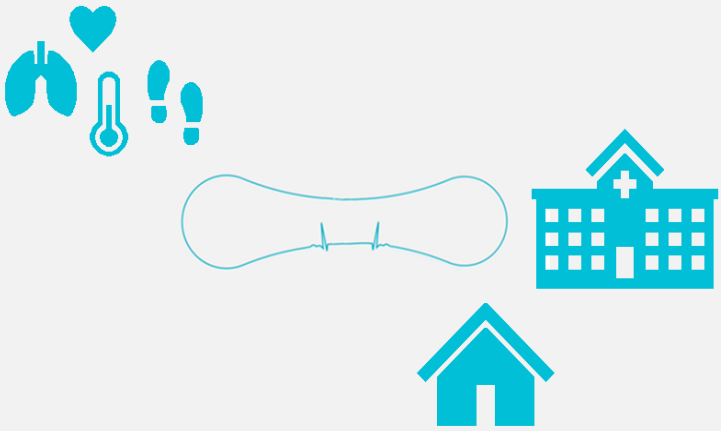
Non-invasive wireless and continuous monitoring of vital signs using a wearable sensor: technical and clinical feasibility



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Preface

The work that lies before you is the product of my clinical specialisation internship at the anaesthesiology department of the University Medical Centre Utrecht. I wrote this thesis to obtain the master's degree in Technical Medicine at the University of Twente. I want to thank all my supervisors for all their effort and time! Together we have tackled several obstacles before being able to conduct the home monitoring study.

First of all, I would like to thank Cor Kalkman, for being always enthusiastic about all aspects of research. Thanks for teaching me how to interpret vital signs during and after surgery. Also, I would like to thank Hermie Hermens for the supportive and critical feedback on my work. Martine, thanks for all your guidance during this project. I really enjoyed doing the clinical testing for the Nightingale study together. Mathilde, I would like to thank you for all the feedback you provided, for always taking the time for me! Paul van Katwijk, I really appreciate all your guidance in my personal development during past two years. Lastly, Erik Groot Jebbink, thanks for being part of my graduation committee.

Moreover, I would like to thank all anaesthesiologists for all interesting moments at the operation room. Furthermore, special thanks to all patients that were willing to participate in the home monitoring study, without whom I would not have being able to do this.

In addition, I would like to thank all technical medicine students that I have worked with: Jantine, Vincent, Jeroen, Erik-Jan, Heike, Arne, and especially Lyan, thanks for all the nice lunchbreaks, walks, chocolate milk breaks and our stairs-policy!

Finally, I would like to thank my family, friends and Niels, for always being there for me and for always being optimistic!

Lieke
Utrecht, October 2019

Abstract

Introduction: Continuous and wireless monitoring of vital signs in hospital and at home might help in early recognition of clinical deterioration in high-risk patients. It is necessary to investigate how to use continuous vital signals for prediction of adverse events in patients at the general ward. Besides continuous monitoring at the general ward, monitoring of vital signs in high-risk patients after discharge at home is unknown territory and therefore it is necessary to assess technical and clinical feasibility.

Methods: For the first study, data was used that was retrieved during a previous study with four different wearable sensors in high-risk patients. The sensor Early Warning Score including trends (Trend s-EWS) was calculated and compared for patients with and without adverse event. For the second study, vital signs and activity of patients that follow the enhanced recovery after oesphagectomy (EROES) programme were recorded with a patch sensor (VitalPatch) within hospital and the first week at home. Firstly, the amount of available data was calculated. Secondly, average heart rate (HR), respiratory rate (RR), skin temperature and the number of steps per day were assessed. In addition, distributions of HR and RR and during day and night and for different levels of activity were compared.

Results: The first study showed that the average Trend s-EWS increased towards the event with the biggest increase one hour before the event for both s-EWS and Trend scores, in contrast to patients without event. For the second study 10 patients were included. The amount of available data was above 70% for 7 patients and for 3 patients several data gaps of more than one day were present. These gaps were mainly caused by Bluetooth or internet connection failure. On average, a decrease in HR and RR on average was found, whereas activity increased considerably as compared to within hospital. HR and RR distributions were lower during the night and increased during activity.

Conclusion: The first study showed that the Trend s-EWS may support in detection of adverse events after high risk surgery using continuous monitoring of vital signs at the general ward. It can be used as complement to nurse rounds for early detection of adverse events. The second study showed that it was feasible to measure vital signs and activity after discharge at home using the VitalPatch in EROES patients, as the amount of available data was sufficient for majority of patients. The described pattern of patients with a normal recovery can serve as baseline for future home monitoring studies. More research is necessary, as it is still unknown whether it is possible to early detect clinical deterioration at home.

List of Abbreviations

AE= adverse event
AF = atrial fibrillation
BMI = body mass index
Bpm = beats per minute
Brpm = breaths per minute
CSV file= comma-separated-values file
ECG = electrocardiogram
EHR = electronic health record
ES = EarlySense
EROES = enhanced recovery after oesophageal surgery
EWS = Early Warning Score
HP= HealthPatch
HR = heart rate
IBI = interbeat interval
ICU = intensive care unit
IMCU = intermediate care unit
IQR = interquartile range
MA = Masimo Radius-7
MBS = MediBioSense
MET = medical emergency team
MEWS = modified Early Warning Score
NEWS = national Early Warning Score
ROC= receiver operating characteristic
RR = respiratory rate
RRS = rapid response system
RRT = rapid response team
SD = standard deviation
SDNN = standard deviation of normal sinus beats
s-EWS = sensor Early Warning Score
s-EWS$_{HR}$ = sensor Early Warning Score of heart rate
s-EWS$_{RR}$= sensor Early Warning Score of respiratory rate
s-EWS$_{SpO2}$= sensor Early Warning Score of saturation
SV = SensiumVitals
Trend s-EWS = trend sensor Early Warning Score
UMCU = University Medical Centre Utrecht

Contents

Chapter 1: Introduction

1.1 Early recognition of clinical deterioration

Early recognition of clinical deterioration in patients is key in prevention and management of complications[1]. Complication rates after major surgery between 3-22% have been reported[2][3], of which up to 60% was avoidable[3]. To timely detect such patient deterioration, we may benefit from more frequent monitoring of vital signs [4]. Lighthall et al. showed that 35% of the patients with abnormal vital signs experienced a critical event, compared to 2.5% in patients with normal vital signs[5].

In current practice, the level of vital signs monitoring decreases from the ICU via ward to home. At the ICU or intermediate care unit (IMCU) patients are usually monitored continuously. Conversely, patients at the general ward are only intermittently observed for vital signs such as heart rate (HR), respiration rate (RR) and core temperature. This is typically performed once every 6-8 hours and provides a snapshot of a patient's health condition [6]. Approximately 70% of in-hospital cardiac arrest patients show changes in vital signs 6 hours before arrest[7]–[9]. These adverse events can therefore easily be missed between two measurements[6][10]. Hence, frequent monitoring of vital signs is relevant in early recognition and prevention of deterioration. Although, this is challenging due to infrequent data collection and incorrect or incomplete documentation [1][11][12]. Therefore, patients may benefit from technical solutions that facilitate continuous remote monitoring of vital signs at the general ward or even at home.

1.2 Continuous monitoring at the general ward

Several studies were performed on the effect of continuous measurement of vital signs, showing inconclusiveness about the effect on the length of hospital stay or prevention of adverse events in hospitals [9][13][14]. A recent systematic review confirmed feasibility of continuous vital sign monitoring outside critical care setting and showed improved patient outcomes[15]. An important burden for implementation and reason for failure of continuous monitoring on general wards is alarm fatigue by nurses, caused by a high false alarm rate. Only 15% of the alarms are considered to be clinically relevant [15][16].

Alarm systems that are currently used for continuous monitoring at the ICU cannot directly be used at the general ward as patients are in a different condition and able to move around freely. Therefore a new strategy is needed [17]. Improving detection of deterioration without having many false alarms requires intelligent monitoring systems that use trend values or integrate multiple vital signs [18]. Churpek et al. reported that adding vital sign trends over time improved prediction of clinical deterioration [19]. This suggests that trend information needs to be incorporated into prediction models to improve accuracy. Before implementation of continuous monitoring at the general ward, it is necessary to investigate how to use these continuous signals for prediction of adverse events. Therefore, the question of the first study was:

1. *Does including vital sign trend information to an Early Warning Score improve the predictive accuracy for adverse events in patients after high risk surgery?*

1.3 Continuous monitoring at home

Patients are discharged earlier than ever before due to the development of for example the enhanced recovery after oesophagectomy (EROES) programme. These explicitly aim to limit the duration of hospital stay and thus might shift the first occurrence of complications to the home setting. Home monitoring enables healthcare professionals to extend patient observation after hospital discharge. This could facilitate quicker detection and thereby enables early diagnosis and intervention, which may improve patient outcome. However, home monitoring of patients after high-risk surgery is unknown territory. In addition, normal recovery pattern for vital signs after discharge is unknown and thereby also for patients that clinically deteriorate. The second study assessed technical and clinical feasibility of home monitoring in patients after high-risk surgery. Therefore, the two questions of the second study were:

2. *To what extent is it technically feasible to continuously and accurately measure vital signs at home with the VitalPatch sensor in EROES patients during the first week after discharge?*

3. *Is it possible to describe a typical 'normal recovery' pattern in terms of vital signs and physical activity in EROES patients during the first week after discharge home?*

The first question was addressed in chapter 3, whereas chapter 4 answers the second and third questions. As a fundament for both studies, chapter 2 provides a clinical background about the predictive value of vital signs and its natural variation.

Chapter 2: Clinical background

Both studies described in this thesis encompass continuous monitoring of vital signs, either at the general ward or at home after discharge. As a fundament, this chapter provides a clinical background about the predictive value of vital signs for adverse events and its natural variation.

2.1 Predictive value of vital signs

Vital signs such as heart rate (HR), respiratory rate (RR) and core temperature are typically measured once per nurse shift, since clinical deterioration is often preceded by a change in vital signs[5]. A change in HR might result from several physiological and pathological conditions, as it is regulated by a comprehensive hormonal and neuronal system which depends on the body's activity level. A lower HR was found to be associated with a better patient outcome than higher rates. Mortality was lowest for a HR of 50-59 min^{-1}, with a step-wise increase for increasing HR[20][21]. Although the gold standard in cardiology is to use 12 leads ECG, one ECG lead providing HR and interbeat interval (IBI) time may be used to detect some cardiac pathological conditions such as arrhythmia[22].

A change in RR is often the first sign of clinical deterioration as the body attempts to maintain oxygen delivery to tissues[23]. Deterioration in respiratory function is one of the most common reasons for ICU admission. Bradypnea and tachypnoea have been found to be strong predictors for adverse events [6][19][25]–[27]. Therefore, early recognition of respiratory dysfunction may help reduce ICU admission and the need for ventilation assistance[6]. Changes of 3 to 5 brpm can be early signs of deterioration[23]. Oxygen saturation will still be normal in early stages of deterioration, while RR increases due to inadequate oxygen delivery to the tissue[17][28]. As intermittent RR measurements can be affected by anxiety or activity and are often poorly performed, continuous monitoring is relevant to monitor decline or recovery[23].

An abnormal (core) temperature, either increased or decreased, is identified as a risk factor for cardiac arrest[29]. Increasing the body's temperature is one of the first mechanisms in response to illnesses such as infections[30]. In contrast, a decrease in body temperature can be seen in late stage infectious disease or blood depletion conditions. In addition, specific drugs or toxins may lower body temperature[22]. Nurses often use tympanic membrane ear temperature measurements, while most wearable devices only offer skin temperature measurement. Skin temperature is typically lower than core temperature and depends on measurement location and body posture. In addition, it is less stable as thermoregulation controls core temperature. Skin temperature is influenced by blood circulation, HR and metabolic rate. In addition, ambient temperature, air circulation and humidity also affect skin temperature[31]. The interpretation of skin temperature in clinical setting has not yet been thoroughly explored.

2.2 Variation in vital signs

Vital signs such as HR and RR after surgery show in-person and between-person variation. Figure 2.1 depicts HR and RR found in three studies, measured in patients on general wards and the medium care[32][33][34]. The mean HR was similar for all three studies, whereas RR showed variation between

the three studies. RR measurements show large inter-observer difference and have a tendency to be 18, 20 or 22 brpm, since it is often estimated by nurses as it still requires manual measurement [35][36].

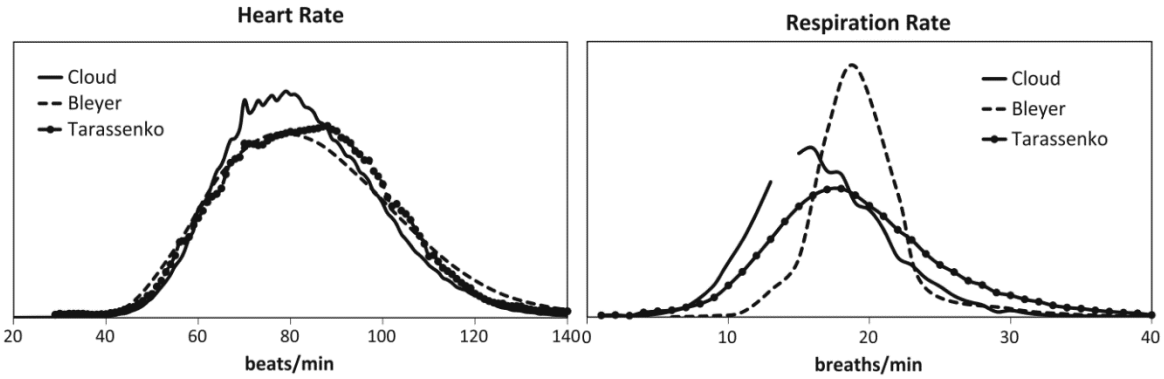

Figure 2.1 Distribution of HR (left) and RR (right) in patients at the general ward or medium care [33].

In addition to HR and RR variation between patients, these vital signs also show variation during the day. As shown in figure 2.2, HR follows a circadian rhythm, showing a decrease during the night and increase during the day. HR and RR are increased during activity. Besides, the circadian pattern is a result of the sleep-wake cycle, originating from the suprachiasmatic nuclei of the anterior hypothalamus. This causes secretion of melatonin, which peaks during the night [37]. The largest increase in HR due to circadian rhythm is present in the morning. It increases with about 25 Bpm from 01:00 to 07:00, with the steepest increase per hour in the morning (05:00) is up to 10 bpm [38]. Heckman et al. showed no significant overall pattern in circadian variation of RR, but it varies on average with 2 brpm during the day[39]. In healthy subjects, skin temperature varies on average with 2 degrees Celsius, with its maximum between 00:00 and 03:00. Subsequently, the skin temperature decreases until it reaches its minimum value around 09:00[40].

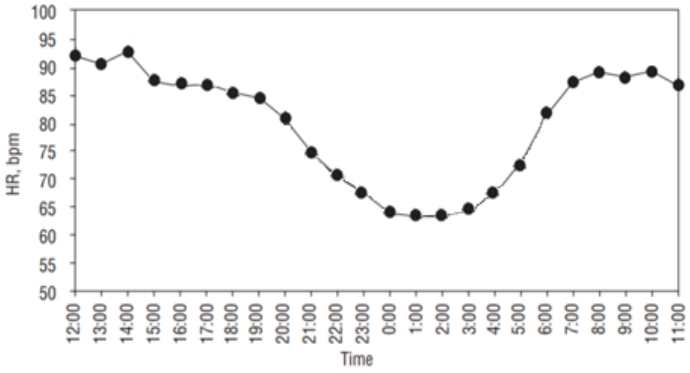

Figure 2.2 Circadian rhythm of HR in healthy controls, modified from [38].

Chapter 3: A new Early Warning Score including trend information for adverse event detection in patients after high-risk surgery

3.1 Introduction1

3.1.1 Early Warning Score

Rapid response systems (RSS) and medical emergency teams (MET) have been introduced in hospitals in order to improve detection of patient deterioration[41][42]. Without adequate and timely MET response, “failure-to-rescue” (FTR) may still occur, which is defined as hospital deaths after adverse events such as a postsurgical complication[43]. Track-and-trigger systems have been developed to prevent delayed MET activation, which is associated with a higher mortality rate [44]. These systems are often based on early warning scores (EWS). Even though EWS systems have been globally adopted, unplanned ICU admissions, cardiac arrest and unexpected deaths were not significantly affected [6][42][45].

3.1.2 EWS after surgery

After surgery, patients frequently show variation in vital signs due to pain, volume shifts and a generalized inflammatory state. Therefore, the EWS is often elevated post-operatively. Figure 3.1 shows average maximum EWS in patients after surgery without complications. Clearly, steepest decrease takes place in the first four days [46].

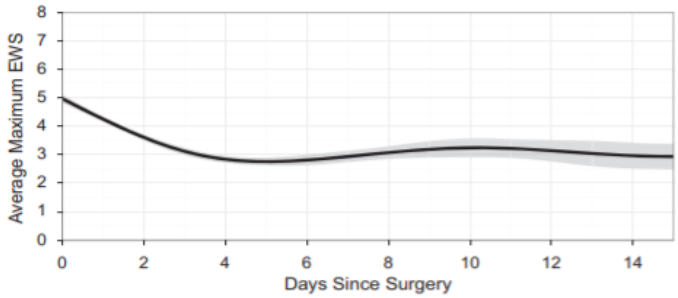

Figure 3.1 Early Warning Score (EWS) after surgery in patients without complications after gastrointestinal and oncology surgery[46].

Hollis et al. studied the relationship between the EWS values and the timing of complications after gastrointestinal and oncology surgery[46]. Figure 3.2 shows the maximum EWS of patients with and without complications during the four days before discharge or before the complication[46]. Average maximum EWS is substantially higher for patients that have higher grade complications. Even though the EWS is increased before adverse events, patients without event show notably higher scores as well. As EWSs are often intermittent and user dependency, detection of patient deterioration can be improved by automation and continuous monitoring[1][11][12]. In addition, as vital sign trends improve prediction of clinical deterioration, trend information needs to be incorporated into a new warning score to further optimize detection of adverse events[19]. Therefore, the aim of this chapter was to study a new early warning score inlcuding trend information using currently available sensors at the general ward.

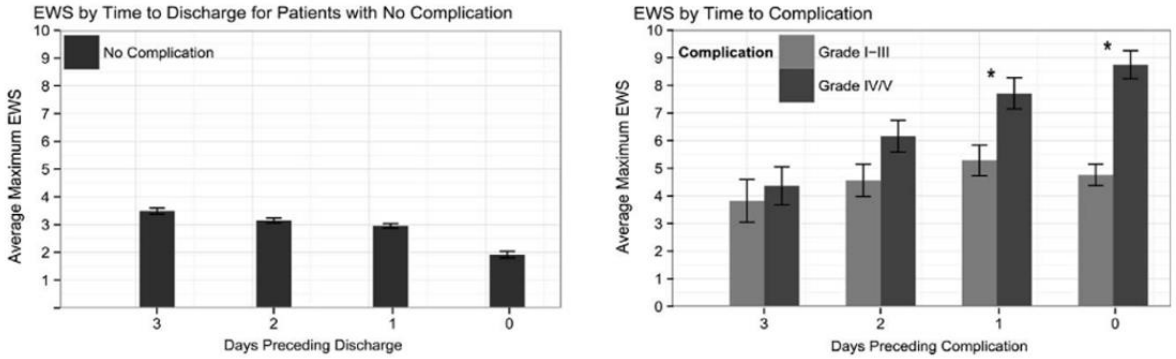

Figure 3.2 Left figure: Average maximum Early Warning Score (EWS) of patients without complication during days before discharge. Right figure: Average maximum EWS of patients with complication[46]*. Complications were graded using the Clavien-Dindo system.*

3.2 Methods

3.2.1 Study population

For this study we used data that was retrieved during a clinical validation study with continuous vital signs recording in high-risk patients (University Medical Centre Utrecht, study number: 16/062). Vital signs were measured in 33 patients who were admitted to the Intermediate Care Unit (IMCU) for the specialisms traumatology or surgical gastro-intestinal oncology during the initial days of recovery at the IMCU, traumatology ward and surgical gastro-intestinal oncology ward by four wireless monitoring sensors and a reference monitor.

3.2.2 Wireless monitoring sensors

Four sensors from different manufacturers simultaneously recorded vital signs. Table 3.1 shows which vital signs were measured by the different sensors. In addition, it shows the sample rate for each sensor.

Table 3.1 Overview of used sensors, with their measures and sampling rate.

	Abbreviation	Sensor type	Measured vital signs	Sampling rate
Masimo Radius-7 **(Masimo Corporation, Irvine, CA, USA)**	MA	Patient-worn monitor connected to a pulse oximeter and acoustic adhesive sensor in the neck	Heart rate (pulse rate) Respiratory rate Saturation	Once per second
SensiumVitals **(Sensium Healthcare Ltd, Oxford, UK)**	SV	Wireless adhesive patch sensor on chest	Heart rate Respiratory rate Axillary skin temperature	Once per two minutes
HealthPatch MD **(VitalConnect, San Jose, California, USA)**	HP	Wireless adhesive patch sensor on chest	Heart rate Respiratory rate Skin temperature	Once per four seconds
EarlySense system **(EarlySense Ltd, Ramat Gan, Israel)**	ES	Contactless piezoelectric sensor under the patient's mattress	Heart rate Respiratory rate	Once per minute

3.2.3 Data selection

Vital signs of patients with adverse events were analysed and compared with patients without events. An adverse event was described as a complication that required intervention. The occurrence of adverse events was identified by the researcher using the electronic health record (EHR) information, including diagnostic reports of an X-thorax, ECG, CT-angiography and clinical notes. The onset of the events was defined as the moment of the entry of the reports including the diagnostic information.

Vital signs of all patients with adverse event were compared with vital signs of patients without event. The latter, hereinafter referred to as "non-event", was selected according to the same time window and number of days postoperatively as the event. So, for each event a non-event window was selected, since both day after surgery and time (e.g., day or night) might influence the height of vital signs due to the recovery process and circadian rhythm. Patients were excluded for a particular sensor, when there was no data available two hours before the event.

3.2.4 Missing data

As data gaps potentially result in missing adverse events, the percentage of missing data of HR, RR and SpO_2 was assessed, for both events and non-event data. A timeframe of 8 hours before the event and non-event was chosen, further explained in 3.2.5.

3.2.5 sensor Early Warning score

Vital signs of all included adverse events and non-events were compared by using a new type of warning score based on continuous wireless sensor data. A time frame of 8h before the events and non-events was chosen, as several studies showed that adverse events show changes in vital signs 6 hours before [7]–[9]. As the sensors do not measure all vital signs included in existing Early Warning Scores, the warning score assigned here is the sensor-EWS, or s-EWS. The s-EWS includes scores for HR, RR and SpO_2. The latter was only measured by Masimo Radius-7. The corresponding s-EWS values for each vital (s-EWS_{HR}, s-EWS_{RR} and s-EWS_{SpO_2}) are displayed in table 3.2. Table 3.2 s-EWSs The s-EWS based on Masimo Radius-7 measurement was calculated with and without SpO_2. The maximum s-EWS is 6 for HR and RR and 9 when SpO_2 is included as well. The s-EWS is the sum of each s-EWS component:

$$s\text{-}EWS = s\text{-}EWS_{HR} + s\text{-}EWS_{RR} (+ s\text{-}EWS_{SpO_2}) \quad \text{equation 3.1}$$

Table 3.2 s-EWSs for each vital sign included in the s-EWS. Thresholds were based on the thresholds used for the National Early Warning Score[47].

Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Respiration rate (brpm)	≤8		9-11	12-20		21-24	> 29
Heart rate (bpm)	< 40		41-50	51-90	91-110	111-130	> 130
Saturation (%)	≤ 91	92-93	94-95	≥96			

In clinical practice, as no continuous monitoring takes place at the general ward and IMCU, it is unknown how to take into account these continuous vital signs. Therefore, two strategies to calculate the s-EWS were compared.

Method 1

Using the first method, the s-EWS was calculated for each complete sample. Samples which were not complete for all s-EWS components were excluded. Subsequently, all s-EWSs within one hour were averaged, resulting in one average s-EWS value for each hour. This s-EWS is not necessarily an integer, but can have one decimal.

Method 2

For this method, the median was calculated for each vital sign per hour, to calculate s-EWS. Therefore, this s-EWS always results in an integer.

3.2.6 Trend score

In addition to the s-EWS, trend scores were assigned for increasing or decreasing vital signs. For every hour, the median of each vital sign was compared to the median value from the previous hour. The delta of these two medians was used for the 'Trend score' (Table 3.3). For saturation only a decrease was taken into account, as increase indicates normalisation.

Table 3.3 Trend scores for each vital sign. Values indicate the absolute difference in corresponding vital sign measurement (median value) of two subsequent one-hour windows. For saturation only a decrease was taken into account.

	0	**1**	**2**	**3**
Respiration rate (brpm)	<2	≥ 2 & < 4	≥ 4 & < 6	≥ 6
Heart rate (bpm)	<5	≥ 5 & < 10	≥ 10 & < 15	≥ 15
Oxygen saturation (%)	<2	≥ 2 & < 3	≥ 3 & < 4	≥ 4

As a trend in vital signs does not necessarily mean that a patient is deteriorating, an extra multiplication factor for the trend scores for HR and RR was included. An increasing trend for a low value indicates normalisation and is therefore less worrisome than an increasing trend for a high value. Therefore, the height of this factor depends on the area in which the vital sign is located (green, yellow, orange or red, based on the thresholds of s-EWS). Figure 3.3 shows the multiplication factor (M_{HR} or M_{RR}) for the Trend score, being either 0, 1.0 or 1.5. The trend score was multiplied with this factor and eventually the sum of the Trend scores were combined with the s-EWS, resulting in the '*Total Trend s-EWS'*:

$$\text{Trend s-EWS} = \text{s-EWS} + (\text{Trend}_{HR} \cdot M_{HR}) + (\text{Trend}_{RR} \cdot M_{RR}) + \text{Trend-SpO}_2 \qquad \text{equation 3.2}$$

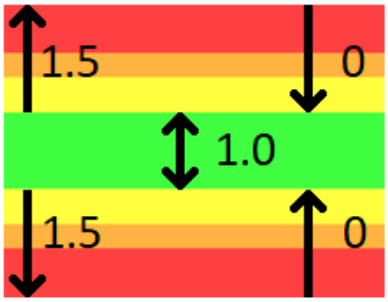

Figure 3.3 Multiplication factor for Trend scores. The multiplication factor is 1.5 for an increase above the green area, or a decrease in the area below the green area. A decrease above the green area or an increase in the area below the green area result in a multiplication factor of 0. Trends within the green area correspond to a factor of 1.

The average s-EWS (method 2), Trend score, and total Trend s-EWS were compared for all event and non-event windows. In addition, the standard deviation (SD) was calculated per hour.

3.2.7 Statistical analysis

To evaluate clinical implications of the use of s-EWS and Trend s-EWS, a receiver operating characteristic (ROC) curve for each sensor was constructed, for which both the false positive rate and true positive rate were calculated. This was performed using all (Trend) s-EWS values of one hour before the events and "non-events". To calculate this, Thresholds of (Trend) s-EWS ranged from 0 up to the maximum score with a step size of 0.5. Subsequently, the area under the ROC-curve (AUC) was calculated for each sensor. In addition, the AUC was calculated for each individual component of the Trend s-EWS per sensor.

3.3 Results

3.3.1 Patient demographics

Table 3.4 shows the patient characteristics of all included patients. In total, 22 adverse events occurred, ranging from 1 to 3 adverse events per patient (table 3.5). Figure 3.4 shows the inclusion of patients for analysis per sensor. 4 events were excluded for analysis, as no recording was available in the period before the onset. Besides, adverse events were excluded individually per sensor, as monitoring did not take place for that particular sensor 2 hours before the event. 72 % (13/18) of the adverse events were diagnosed during daytime (06:00-18:00), and 44 % (8/18) of the events were identified in the morning (06:00-12:00).

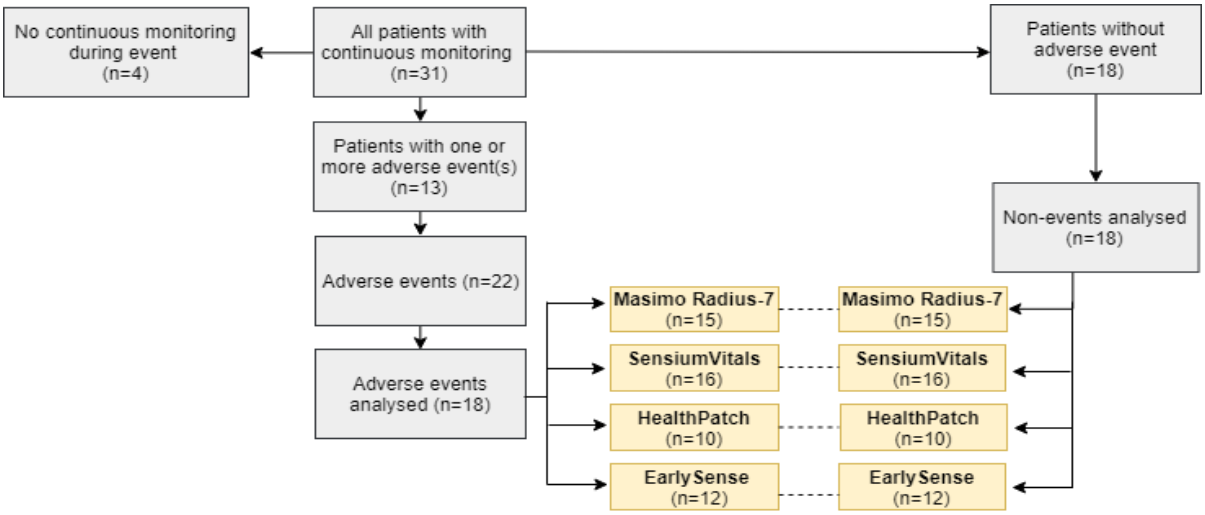

Figure 3.4 Inclusion of patients for analysis per sensor. Both events and non-events were included for analysis.

Table 3.4 Patient characteristics for all patients with and without an adverse event that were included for analysis. n: number, BMI: body-mass index. IQR: interquartile range.

		All patients (n=24)	**No adverse event** (n=12)	**Adverse event** (n=12)
Age (years) *Median (IQR)*		62 (20)	57 (16)	68 (22)
Sex *n (%)*	Female	11 (46)	5 (42)	6 (50)
	Male	13 (54)	7 (58)	6 (50)
BMI (kg/m²) *Median (IQR)*		27 (4)	27 (4)	27 (5)
Speciality *n (%)*	Surgical Gasto-intestinal oncology	12 (50)	4 (33)	8 (67)
	Traumatology	12 (50)	8 (67)	4 (33)
Length of stay (days) *Median (IQR)*		14 (10)	12 (10)	18 (11)

Table 3.5 Number and type of adverse events that were included for analysis.

Event	**Number of events**
Atrial fibrillation	4
Pneumonia	3
Pneumothorax	3
Distended stomach tube	2
Pulmonary Embolism	1
Respiratory insufficiency	1
Bowel herniation	1
Pancreatitis	1
Chyle leak	1
Anastomotic leak	1

3.3.2. Missing data

Figure 3.5 shows the average percentage of complete s-EWS samples for each sensor of all event and "non-event" 8-hour windows. Masimo Radius-7 and HealthPatch clearly had fewer missing data than SensiumVitals and EarlySense. In addition, it is notable that available data for HR was much higher than RR for Masimo, SensiumVitals and EarlySense.

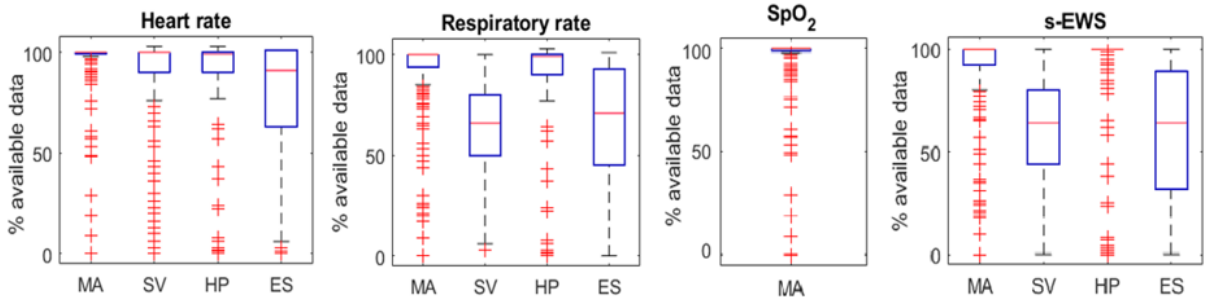

Figure 3.5 Available data of all events and "non-events" (8-hour windows), displayed for HR, RR, SpO_2 and complete s-EWS. Top and bottom edges of the blue box indicate 25th and 75th percentiles and the whiskers extend to the most extreme points not considered outliers. Outliers are indicated by the red plus-sign. MA=Masimo Radius-7, SV=SensiumVitals, HP=HealthPatch, ES=EarlySense, SpO_2: oxygen saturation, s-EWS: sensor Early Warning Score.

3.3.3 s-EWS different strategies

Using method 1 and 2 resulted in slightly different s-EWSs. Especially when a vital sign fluctuates around an s-EWS threshold value (i.e., RR=20 brpm) or when outliers are present. Figure 3.6 shows an example of an RR signal fluctuating around a threshold value. Using method 2, an abrupt increase in s-EWS_{RR} from 0 to 2 during the last hour was present, while for method 1 the increase in s-EWS_{RR} was more slowly.

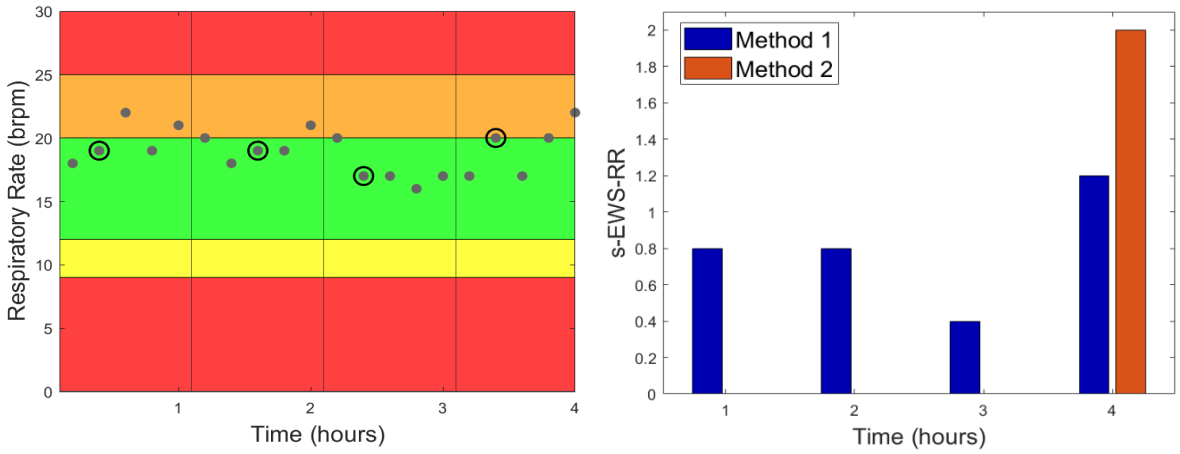

Figure 3.6 Left figure: Example of a respiratory rate signal. The green, yellow, orange and red colour indicate s-EWS_{RR} scores of respectively 0,1,2 and 3. The median value per hour is indicated by the surrounding circle. Right figure: s-EWS_{RR} using both method 1 and 2.

Figure 3.7 depicts an example of an RR signal that includes measurement outliers, which shows that the s-EWS_{RR} score using method 1 ranges from 0.2-1, while for method 2 the score is 0. Using method 2 results in an integer (being 0,1 or 2), while the result of method 1 is an average and can take intermediate values due to averaging of all samples. An outlier directly influences the height of the s-EWS when calculated with method 1, which is not the case using method 2. Method 2 was chosen for further analysis, as the influence of outliers is less than for method 1.

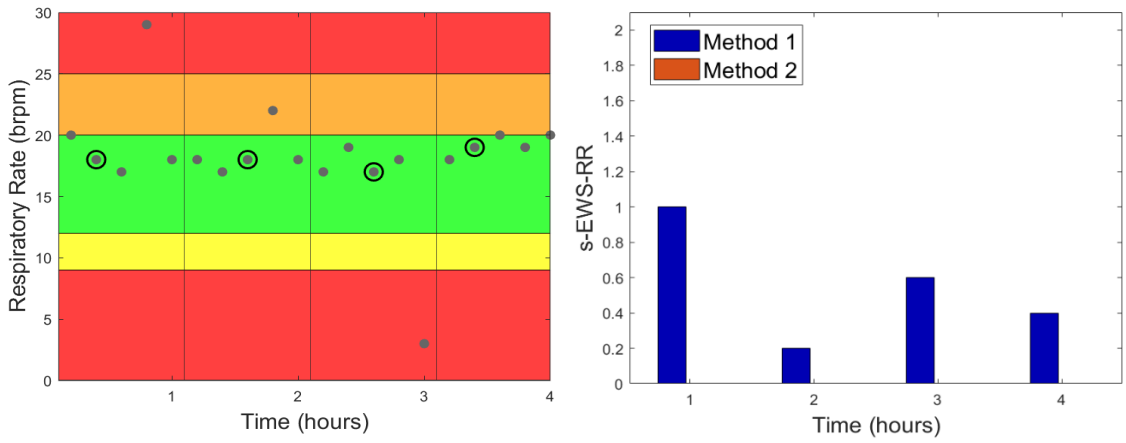

Figure 3.7 Left figure: Example of a respiratory rate signal with outliers. The green, yellow, orange and red colour indicate s-EWS$_{RR}$ scores of respectively 0,1,2 and 3. The median value per hour is indicated by the surrounding circle. Right figure: s-EWS$_{RR}$ using both method 1 and 2.

3.3.4 s-EWS: events and "non-events"

Figure 3.8 shows the average s-EWS (method 2) for patients with and without event. The average s-EWS of the event-group was clearly higher than for the non-event group. An increasing total s-EWS towards the event was present, of which HR was the biggest contributor. This is clearly different from the non-event group, where the EWS contribution of HR is much smaller and fluctuating instead of increasing towards the end of the window. Furthermore, differences between both groups were considerable larger for HR than for RR. Notably, s-EWS based on HealthPatch measurements was much higher than the other three sensors.

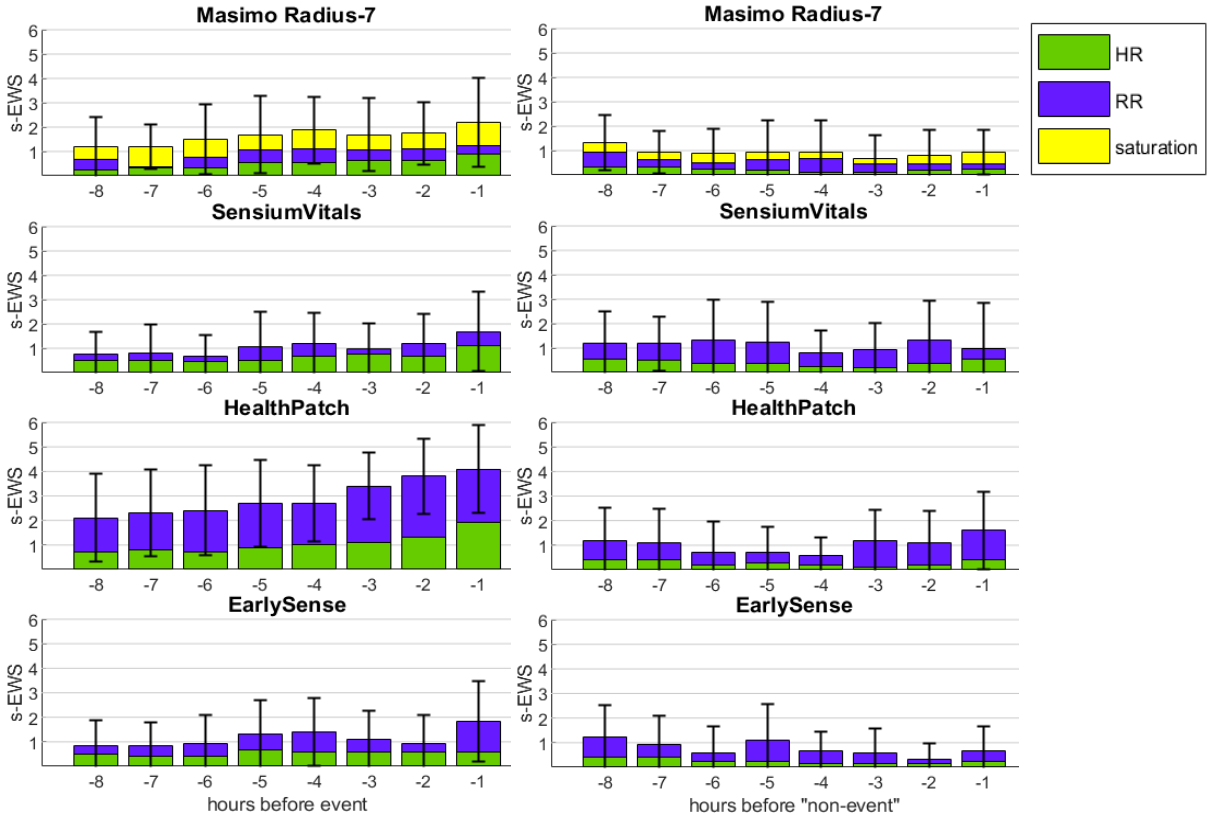

Figure 3.8 Average s-EWS of all patients with event (left) and without event (right) 8 hours before the event and non-event. The vertical black lines indicate one standard deviation. The standard deviation for Masimo Radius-7 of the s-EWS includes SpO_2.

Moreover, the standard deviation was bigger for patients with events as compared to patients without events, except for SensiumVitals measurements. Even though s-EWS based on Masimo Radius-7 recordings showed a considerable increase for the events when including saturation, s-EWS for the patients without events was higher as well. In contrast to the non-event group, scores of s-EWS$_{SpO2}$ of 2 and 3 were assigned one hour before the event.

3.3.5 Trend scores: events and "non-events"

Figure 3.9 shows the average Trend scores for patients with and without event. Trend scores based on all four sensors showed an increasing trend towards the event, having its highest score one hour before the event. For the events, HR and RR increase were the biggest contributors for the total Trend score. Notably, a local maximum around 6 and 5 hours before the event was present, after which the Trend scores slightly decreased. It is notable that for the patients without event, all sensors showed relatively high Trend scores one hour before the "non-event". Generally, standard deviations were higher for patients with event, except for scores based on SensiumVitals.

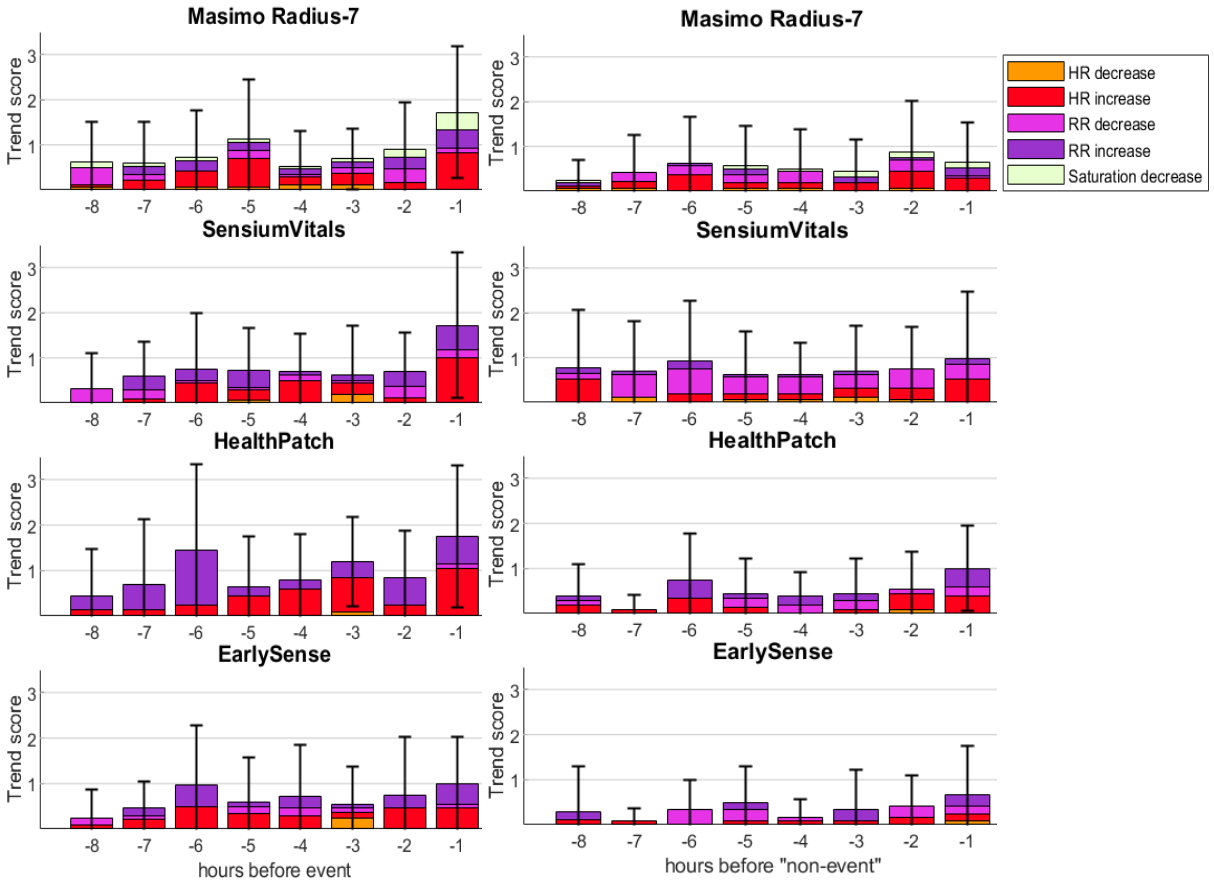

Figure 3.9 Average trend scores of all patients with event (left) and without event (right) 8 hours before the event and non-event. The vertical black lines indicate one standard deviation.

3.3.6 Trend s-EWS: events and "non-events"

Figure 3.10 shows the average total Trend s-EWS and its standard deviation for patients with and without event. Scores based on all sensors for the events were equal to or higher than 3, whereas for the "non-events" the scores were always below 3. The biggest average increase for Trend s-EWS was present during the last hour before the event. The standard deviation was generally higher for the events, as compared to the non-events.

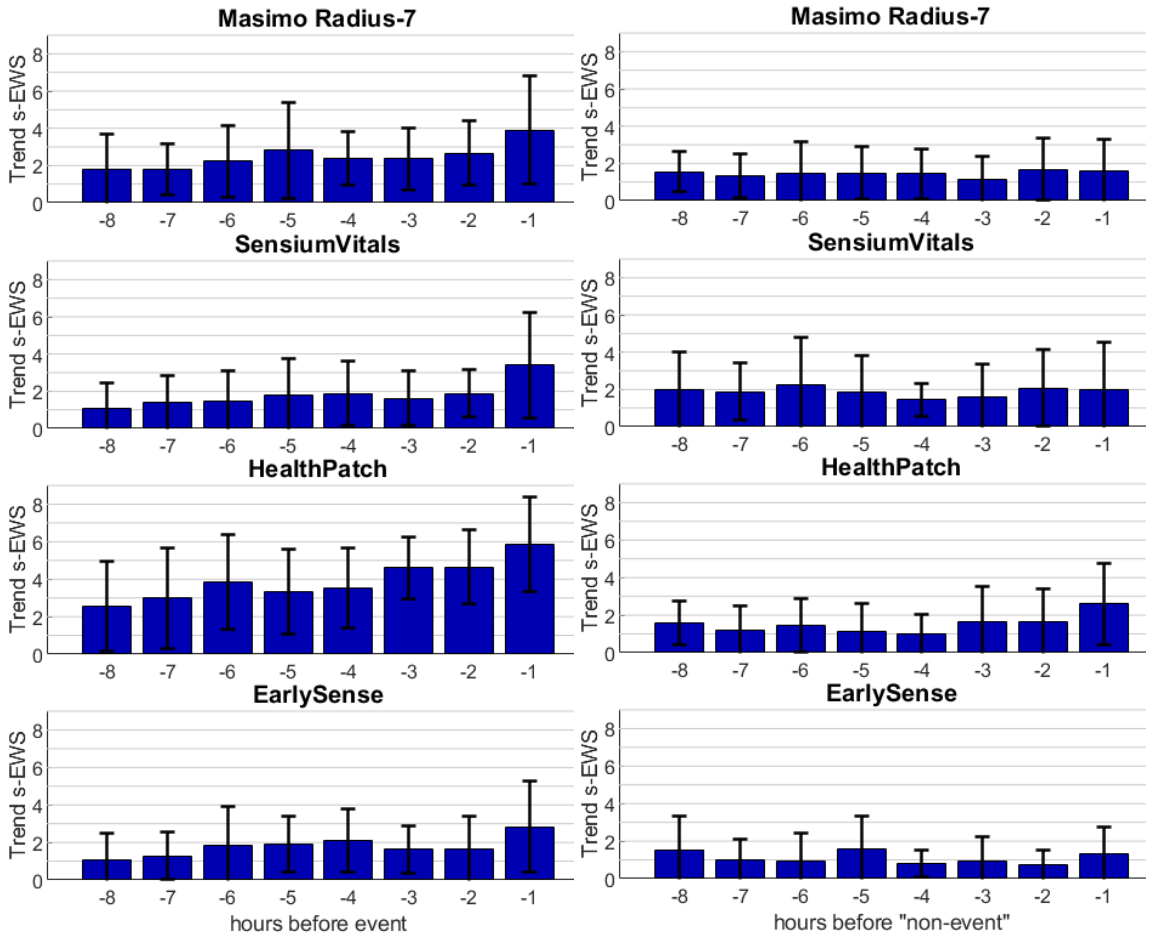

Figure 3.10 Average total Trend s-EWS of all patients with event (left) and without event (right) 8 hours before the event and non-event. The vertical black lines indicate one standard deviation.

3.3.7 Clinical implication of the (Trend) s-EWS

Figure 3.11 shows the ROC-curves with AUC for all sensors for both s-EWS and Trend s-EWS. The AUCs differed considerably for each sensor. Including trend scores into the s-EWS increased AUC for measurements with Masimo Radius-7 (with and without saturation) and SensiumVitals. In contrast to the s-EWS, including trend scores for SpO_2 in the total Trend s-EWS increased the AUC for Masimo Radius-7. AUC for different components of Trend s-EWS are displayed in table 3.6, which showed considerably higher AUCs for HR as compared to RR.

*Table 3.6 AUC per sensor for different components of the Trend s-EWS. *= (Trend) s-EWS scores based on Masimo Radius-7 measurements without saturation.*

Vital sign	**Sensor**			
	Masimo Radius-7	**SensiumVitals**	**HealthPatch**	**EarlySense**
Trend s-EWS components				
s-EWS	0.70 (0.70*)	0.66	0.86	0.70
s-EWS$_{HR}$ + Trend HR	0.75	0.69	0.83	0.71
s-EWS$_{RR}$ + Trend RR	0.64	0.60	0.69	0.69
Trend scores	0.71 (0.66*)	0.65	0.64	0.62
Trend s-EWS	0.74 (0.72*)	0.68	0.84	0.69

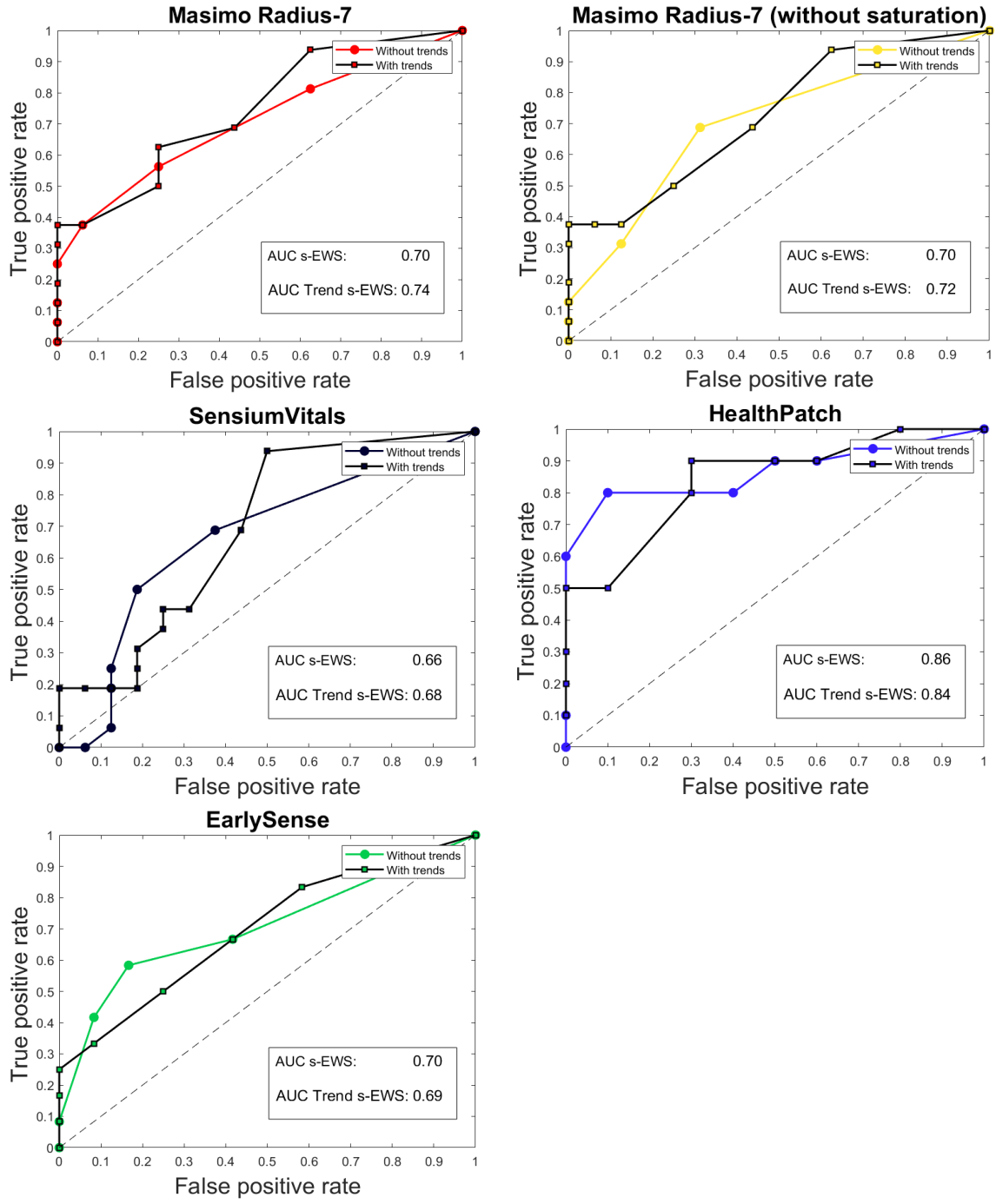

Figure 3.11 Receiver-operating curves of s-EWS and Trend s-EWS for all four sensors. For Masimo Radius-7, ROC both with and without saturation are displayed.

3.4 Discussion

This was the first study in which a static and trend-based warning score in relation to adverse events was studied for multiple wireless sensor types at the general ward. We showed the potential ability of the (Trend) s-EWS based on continuous wireless sensors to discriminate between patients with and without adverse events. Including Trend scores into the s-EWS further improved results based on Masimo Radius-7 (with and without saturation) and SensiumVitals recordings emphasizing the relevance of trends in vital signs.

Additional value of trend information

On average, higher Trend scores were present in patients with events. However, not all events had a high Trend score, and some patients without events had considerable Trend scores. Prediction of adverse events based on measurements with EarlySense and HealthPatch did not improve after including trend information in the warning score. Some high Trend scores were possibly caused by inaccuracy of the measurement or the limited number of data samples, which was the case for some measurements with SensiumVitals and EarlySense. As simultaneously recorded vital sign measurements by the other sensors did not result in these high Trend scores in these situations, these false Trend scores may be explained by unreliable vital sign recordings. This affected the results substantially, as the number of included recordings was limited.

In addition, the current study showed a clear increase in Trend s-EWS score one hour before the events, indicating that there is an association between vital sign changes and the development of adverse events. Yet, a local maximum was observed five to six hours before the event, suggesting that events could be detected more than one hour before the event, which is in accordance with literature[7]–[9]. The definition event occurrence was based on information in the EHR, for example ordering a chest X-ray, ECG or CT-angiography. The registration, however, was not exact and depended on the timing of the nurse recording a diagnostic test in the EHR, which may have been delayed in some cases. Possibly, the onset of some events was before the recorded time in the EHR.

In contrast to our expectations, the non-event group showed considerably large Trend scores as well. It was expected that if large scores were present, scores for both increase and decrease were expected to be comparably large due to natural variation around an equilibrium. However, the average scores for increasing HR Trend were higher than scores for decreasing HR for all non-events, especially one hour before the non-event. This might be explained by the fact that most events took place in the morning, where it is likely that vital signs show natural increase caused by the circadian rhythm and increasing levels of activity. 44% (8/18) patients had their events in the morning (06:00-12:00h) and 72% (13/18) of the adverse events were between 06:00-18:00h. As the timeframe for the non-events were similar to the events, this could explain relatively high scores for increasing trends in the non-event group. In healthy subjects, the steepest hourly increase of HR in the morning (05:00) is about 8-10 bpm[37][38]. Even though this is a natural occurrence, this would result in an s-EWS$_{HR}$ of 1 or 2. Moreover, HR and RR are influenced by activity. Hospitalized patients are expected to be more active in the morning when compared to the rest of the day. Increasing thresholds for Trend scores or correction factors for activity could compensate for these effects on Trend s-EWS, although one should consider a sufficient sensitivity as well. This could possibly be solved by calculating Trend scores over periods longer than one hour. Trends may also be calculated by linear regression using all data instead of the median value. The optimal epoch length for trend scores needs to be determined using a larger data set.

Comparison between sensors

Even though all sensors measured vital signs simultaneously, differences were found in the (Trend) s-EWSs based on each sensor. This is expected to be caused by several aspects.

First of all, different measurement principles of the sensors sometimes affected the height of measured vital signs, and therefore also (Trend) s-EWSs. Masimo Radius-7 measures pulse amplitude of the photoplethysmography signal to determine HR, whereas EarlySense uses cardio ballistic movement, associated with ejection of blood with every contraction. AF with rapid ventricular rate often results in an undetectable peripheral pulse, as ventricular filling time is extremely short. This will result in a lower detected HR for Masimo Radius-7 and EarlySense. HealthPatch and SensiumVitals both use ECG-derived HR estimation, which is much more robust during periods of AF, as it measures electrical activity of the heart and every QRS complex will be captured and used in the calculation of HR. AUC for measurements based on the HealthPatch was therefore clearly higher than for Masimo Radius-7. Since postoperative acute onset AF is common in high-risk surgical patients, this highly influences the ability to predict such adverse events. Moreover, s-EWS_{RR} values based on HealthPatch measurements were considerably higher when compared to the other thee sensors, for both events and non-events. This can be explained, as HealthPatch has been shown to overestimate RR, especially during AF [48].

Secondly, an important reason for the differences between all sensors is the patient population for which recordings of the individual sensors were available. For some patients, sensor recordings were not available, which influenced the average Trend s-EWS. Therefore, based on this study it is difficult to conclude which sensor performs best in prediction of adverse events.

Another important difference is that Masimo Radius-7 is able to measure oxygen saturation. Adding s-EWS_{SpO2} did not improve AUC, whereas adding SpO_2 Trend scores caused an increase in AUC. In contrast to the "non-events", scores of 2 and 3 for SpO_2 were given one hour before the events. This suggests that higher scores reflect clinical deterioration and that it is recommended to use SpO_2 measurements for adverse event prediction with the Trend s-EWS. However, one must also consider that saturation measurements are very sensitive for movement and therefore might often result in measurement outliers.

Besides these differences, an important agreement between the sensor's measurements was found. The AUC for HR was considerably higher than for RR for within this study. This is expected to be caused by the inaccuracy which with RR is estimated when compared to the variation in RR due to the presence of an adverse event. HR is estimated more precisely when compared to the variation within the signal. Moreover, many patients had a respiratory rate that was relatively high when compared to the thresholds for s-$EWS_{RR,}$ which were based on the NEWS threshold for RR[47]. Watkinson et al. determined new thresholds for an EWS based on both continuous measurements and manual measurements. They showed that thresholds for continuous measurements were 4 brpm higher as compared to manual measurements[34]. Using different threshold levels could further optimize prediction of adverse events based on RR.

Strengths, limitations and future perspectives

Several studies investigated the association between the EWS and assessment development of adverse events[34][46][49]. For example, Hollis et al. reported that the EWS was able to identify adverse events of grade IV or V (Clavien Dindo system) with a sensitivity of 81% and specificity of 84%[46]. However, these studies were performed using intermittent vital signs. The current study was unique in using a new warning score including trend information based on continuous vital sign measurement measured in patients at the IMCU and general ward. Continuous recording is valuable, as it facilitates taking a median value over several samples excluding outliers, which results in a more reliable value.

The current study used HR, RR and SpO_2 to calculate a warning score. Besides HR,RR and SpO_2, different versions of an EWS also include presence of supplemental oxygen, core temperature, systolic blood pressure and level of consciousness[47]. These were not included, as automatization and continuous measurement is not possible yet. Watkinson et al. reported that the best performing EWS based systems included an additional score when a patient is given supplemental oxygen support[34]. This requires including information within the EHR into a such a score. Instead of core temperature, HealthPatch and SensiumVitals measured skin temperature, which was not included for analysis in this study. Skin temperature depends on measurement location and is less stable than core temperature, as thermoregulation controls core temperature. It is influenced by blood circulation, HR and metabolic rate. In addition, ambient temperature, air circulation and humidity also affect skin temperature[31]. It is not clear yet how to interpret skin temperature and therefore it was not used for analysis. Although, an increase in (skin) temperature combined with an increase in HR and RR could possibly further improve early detection of events such as pneumonia. However, it is expected that deviation in skin temperature due to an underlying complication is small when compared to factors as circadian rhythm and environmental factors. A deeper understanding of the relation between skin temperature and adverse events is desired. Alternatively, development of wireless non-invasive sensors that estimate core temperature more precisely would promote development of a more sophisticated algorithm.

This study was limited by the number of patients that were included, with one to four cases per adverse event type. To further improve development of algorithms that detect adverse events, it is necessary to collect more continuous vital sign data of patients with adverse events on general wards. Different types of adverse events were recorded by all sensors, of which severity and nature differed greatly. AF is expressed by a sudden increase in HR, whereas pneumonia and anastomotic leak may show a more gradual increase. Therefore, one could suggest categorizing events into sudden onset and non-sudden onset events. In that way, prediction algorithms can be further improved.

To further improve the proposed Trend s-EWS, optimal cut-off points for each vital sign and Trend score need to be found. Thresholds for Trend-scores were based on visual inspection of all event and non-events. For this study, a limited number of events was included. Optimization using this dataset would have resulted in overfitting, which hampers generalization of the algorithm. Therefore, this needs to be done using larger (training and test) datasets with much more events. Future research should also reveal optimal update rate of Trend s-EWS. For example, both short and long terms trends could be taken into account. Subsequently, the clinical value of using a score such as Trend s-EWS needs to be proven statistically.

In the future, a machine learning algorithm might help in prediction of adverse events at the general ward. Kwon et al. Showed that their deep-learning EWS (DEWS) algorithm outperformed the MEWS[50]. It is important to note that such systems do not work perfectly yet as there is not enough available continuous data of patients that develop adverse events at the general ward yet. They are often trained specifically for individual adverse event types. A disadvantage of deep learning methods is that results are not explainable, as the algorithm is a black box. When such a system alarms, a nurse or doctor needs to check the patient before knowing the likely reason for the alarm. Therefore, it is thought that implementation of such techniques in clinical setting is hampered. A simple algorithm with explainable results that can be used for detection of clinical deterioration in general that complements the standard nurse rounds is therefore advised.

3.5 Conclusion

This study showed that the Trend s-EWS may support in detection of adverse events after high risk surgery using continuous monitoring of vital signs at the general ward. Including Trend scores into the s-EWS increased the AUC for the Masimo Radius-7 and SensiumVitals recordings. Furthermore, including Trend scores for oxygen saturation into the total score resulted in an increase in AUC. The AUC for Trend s-EWS_{HR} was higher than for Trend s-EWS_{RR} for all four sensors, which indicates that heart rate seems to be a better predictor for adverse events than respiratory rate using currently available sensors. Trend s-EWS using wireless and continuous vital signs monitors is not yet able to replace nurse rounds but can be used as complement to detect clinical deterioration in high-risk patients at general wards. More research is necessary to further optimize the algorithm.

Chapter 4: Feasibility of home monitoring with the VitalPatch in EROES patients

4.1 Introduction

Home monitoring for patients after surgery is of increasing interest. In general, enhanced recovery after surgery (ERAS) programmes result in improved patient outcome and shorter hospital stay[51]. At home, patients are more active and tend to sleep better [52]. However, some of the benefits of ERAS might be offset by a shift in the occurrence of complications from the hospital to the home setting. In current clinical practice even patients undergoing high-risk surgery such as oesophagectomy are discharged home much earlier than a couple of years ago. Generally, vital signs monitoring is not performed at all after discharge. If a patient develops a surgical complication after discharge at home, the risk of missing the early signs of deterioration is increased. Complication rates for patients that follow enhanced recovery after oesophagectomy surgery (EROES) up to 67% have been found, of which pulmonary complications and anastomotic leakage occur most frequently [53]. Even though EROES is associated with better outcome, readmission rates are still 11-20% within 30 days after discharge [33][37][38][56].

Home monitoring could enable healthcare professionals to extend patient observations to the period after hospital discharge. Remote monitoring, or telemonitoring, could facilitate quicker detection of deterioration and hence promote early diagnosis and intervention. Several continuous monitoring studies at the general ward with wearable monitoring devices have been performed, which showed high usability and acceptability among nurses and patients. [57]–[61].

Most of the wearable and wireless monitoring devices available today were specifically developed for hospital use. The HealthPatch (VitalConnect, Campbell, CA) is such a wearable wireless patch sensor that allows long-term monitoring of patients in their own home setting[57][60]. It was well received by patients as well as nurses, and validated in healthy subjects [58][61]. Moreover, in a methods comparison study, Breteler et al. showed that the HealthPatch measured HR accurately in patients in a surgical step-down unit, whereas RR was outside acceptable limits[48]. The VitalPatch (VitalConnect, San Jose, California, USA) is the successor of the HealthPatch and was updated to improve accuracy of RR during periods of arrhythmia and activity[62]. However, this new respiration algorithm in the VitalPatch has not been validated in clinical settings yet, and it was therefore necessary to test it prior to further clinical research with that device.

Even though the potential of remote vital signs monitoring in hospital setting or in healthy subjects is shown previously, monitoring of vital signs in patients after high-risk surgery after hospital discharge at home is unknown territory. No systems to detect patient deterioration after discharge home have been developed yet. Such monitoring requires a different strategy when compared to the hospital setting, as patients are able to move around in their own home. Before developing algorithms for detection of clinical deterioration at home, it is necessary to describe patterns in terms of vital signs and activity for patients without adverse events. Therefore, the objective of this study was to assess technical feasibility of continuous monitoring with the VitalPatch, aiming to retrieve first experiences

with continuous home monitoring of high-risk patients. In addition, we studied the normal recovery pattern of EROES patients at home in terms of vital signs and activity and assessed by surgeons.

4.2 Methods

4.2.1 Study design and study population

Ethical approval for this study was provided by the medical ethical committee of the UMCU (16/371). This feasibility study has an observational design. Adult patients following the EROES protocol were asked to participate in this study. This patient category was selected, because of the high deterioration rate after oesophagostomy either during hospital stay or in the first days at home after hospital discharge. Exclusion criteria were allergy to adhesives, a wound or skin lesion near the application site and presence of implanted cardiac devices. Patients were approached one week before surgery. Written informed consent was obtained at the IMCU or the general ward.

4.2.2 Description of the sensor

The VitalPatch is the sensor that was used (figure 4.1), a wireless and wearable patch sensor that measures single-lead ECG, HR, interbeat interval (IBI) time, RR, skin temperature, body posture and step count. The VitalPatch needs to be placed on the left pectoral muscle, at a 45˚ angle and has a battery life of 120 hours [61][48]. The patch contains two ECG electrodes with hydrogel, a thermistor, and a zinc-air cell battery. The sensor includes a tri-axial accelerometer and Bluetooth Low-Energy (BLE) transceiver for wireless connection with a relay device. Appendix A describes how the VitalPatch derives HR and RR.

Vital signs measured by the VitalPatch were retrieved using an online web application (*MediBioSense (MBS), Westwoodside UK*), and a mobile phone (CUBOT KingKong) with 3G internet connection. The MBS application automatically connects with a VitalPatch within Bluetooth range (secured by a 24-digit password).

Figure 4.1 VitalPatch being placed on a patient's chest.

4.2.3 Measurement protocol

Figure 4.2 shows an overview of the study protocol. Measurements with the VitalPatch were initiated at the IMCU or general ward, to provide a baseline for the home monitoring study. In addition, to validate RR measured by the VitalPatch, reference measurements were performed during these baseline measurements within hospital with an additional device: Masimo Radius-7, a previously validated wearable monitor. Nurses and surgeons were blinded for the measurement within hospital and alarming was not active. Moreover, patients were blinded for their own vital sign measurements

during the entire study. The researcher checked vital signs measured by VitalPatch at the MediBioSense platform (Appendix B) three times a day and in case of abnormalities, the nurse or surgeon was informed. Patches were replaced after 5 days, as the predicted battery life was 120 hours.

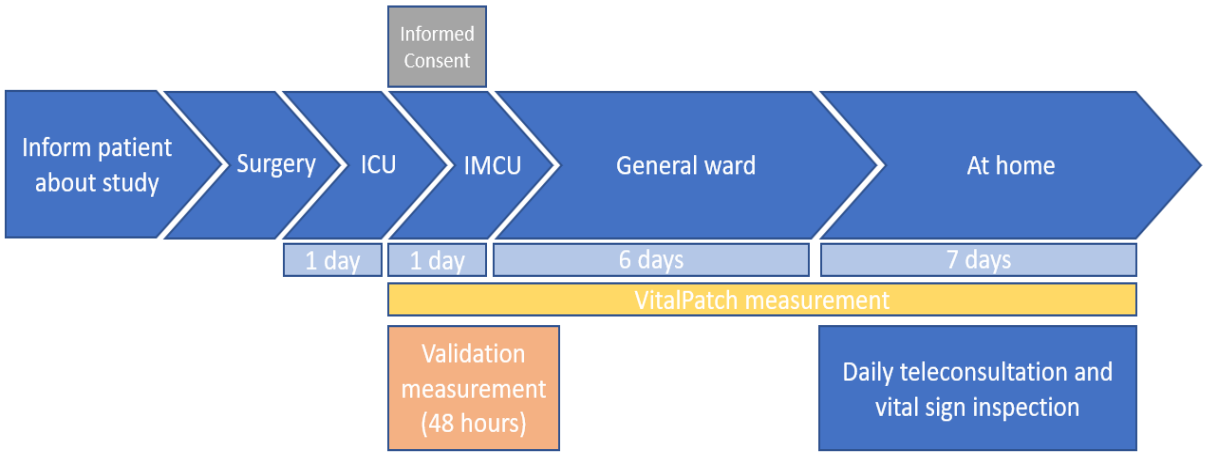

Figure 4.2 Overview of the care pathway for oesophageal cancer surgery

On the day of discharge, patients were provided with a mobile phone (CUBOT, Android 8.0), a charger, a new patch and extra patch. The patients were instructed to replace the patch themselves at home after five days. They were also instructed to always keep the phone charged and within a range of 5 meters from the sensor. Furthermore, instructions to replace the patch at home were provided (Appendix C). Additionally, patients were asked to fill in daily activities and sleep in a diary provided by the research team (Appendix D).

At home, from the day after discharge patients were called daily by a surgeon for seven consecutive days. The expert's view on the patient's recovery (normal or abnormal) was assessed by two warning scores. Questions following a standard list were asked, about general well-being, fever, pain, movement, food, weight, sleep and the patch. Based on each teleconsultation, the surgeon gave a 'score of concern' reflecting the patient's condition (figure 4.3). Subsequently, the surgeon was provided with vital signs by means of a 24-hour display (figure 4.4) and an overview of vital signs of the previous seven days (figure 4.5). Both vital sign displays were created using MATLAB (Version 2018b, The MathWorks, Natick, Massachusetts, USA), which were provided to the surgeon each morning via an encrypted messaging platform for doctors (Siilo, Amsterdam). Median filtering with a 15-minute window was applied for HR, RR and skin temperature. Number of steps taken by the patient were reset at 00:00 daily. After inspection of these vital sign overviews, the surgeon assigned second score of concern based on these vital signs.

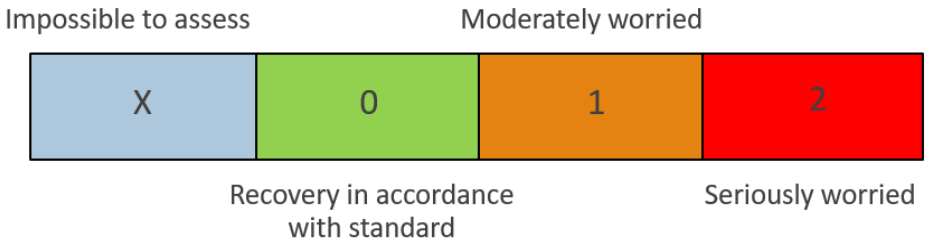

Figure 4.3 'Score of concern' that was given twice by the surgeon: after the teleconsultation and after seeing the vital signs.

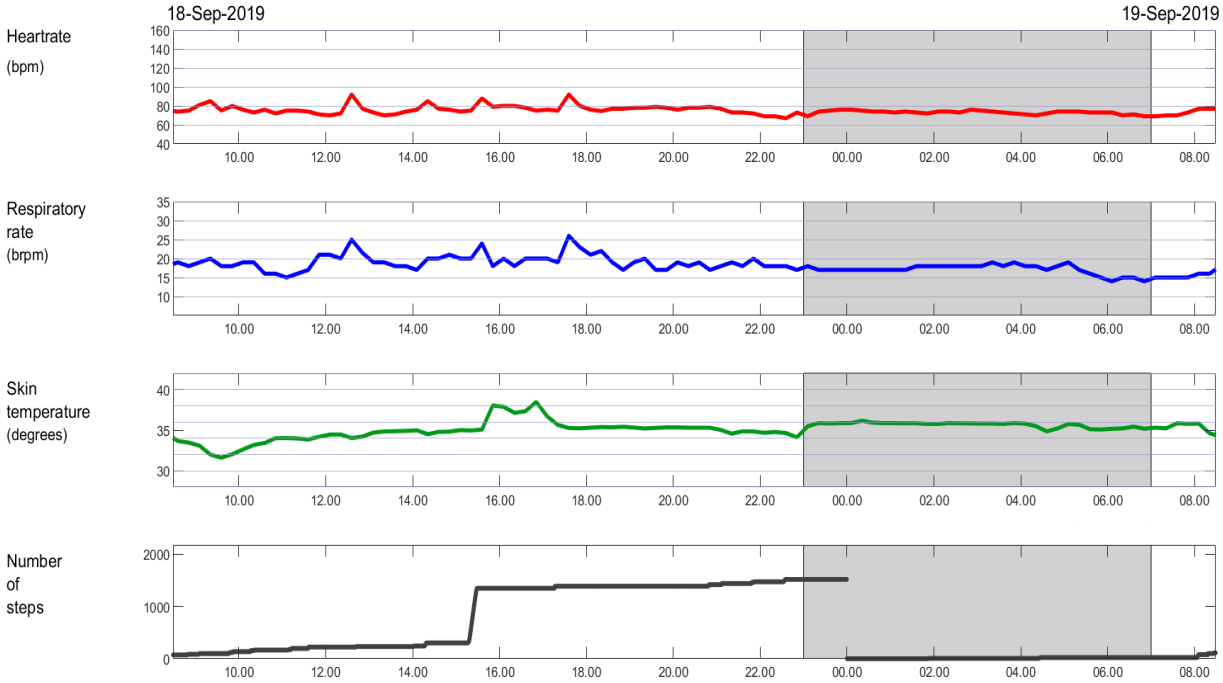

Figure 4.4 Vital sign overview (24h) as provided to the surgeons daily during the home monitoring. The shaded area indicates nighttime. Bpm: beats per minute, bprm: breaths per minute.

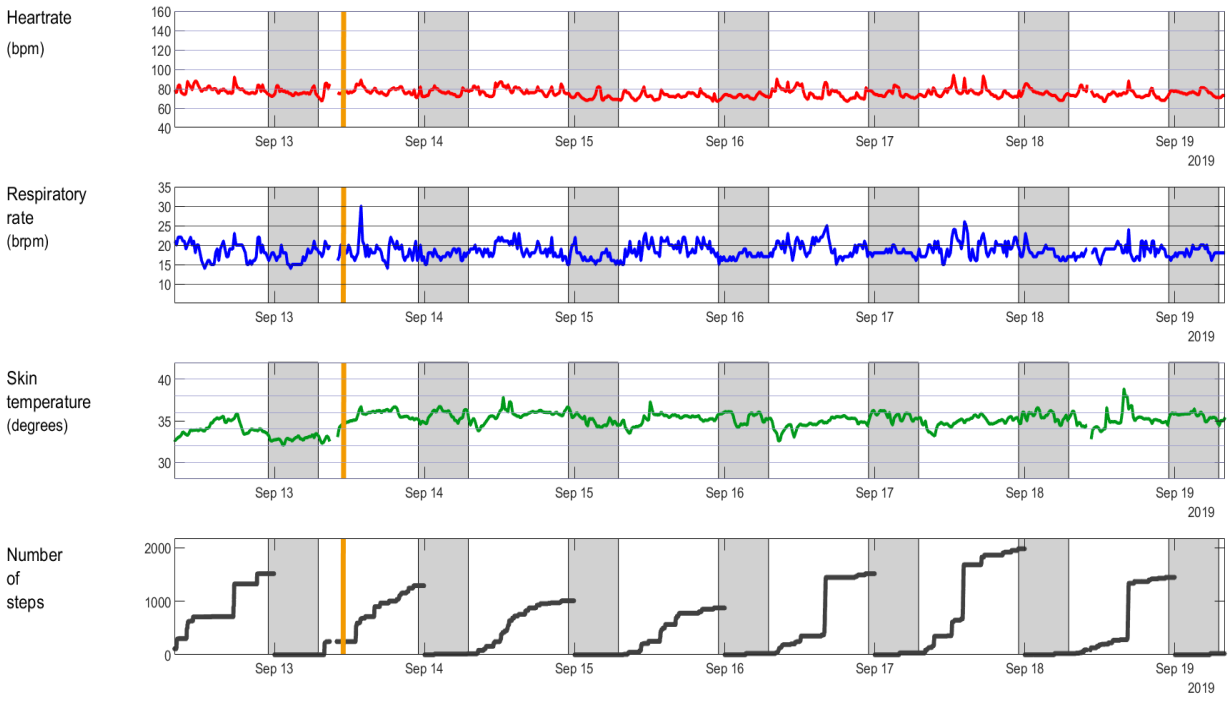

Figure 4.5 Vital sign overview (last 7 days) as provided to the surgeons daily during the home monitoring. The shaded area indicates nighttime. The orange line indicates moment of discharge. Bpm: beats per minute, bprm: breaths per minute.

4.2.4 Analysis: validation measurement

To determine agreement between RR measured by the VitalPatch and Masimo Radius-7 Bland-Altman analysis for repeated measurements was performed. Furthermore, Clarke-Error Grid analysis was performed to assess consequences for clinical decision making. Both methods required the data to be synchronised. Firstly, RR measured by both Masimo Radius-7 and VitalPatch were uniformly sampled. Secondly, RR of Masimo Radius-7 was downsampled to the same sample frequency as VitalPatch (0.25 Hz). Subsequently, both signals were filtered using a 15 minute moving median filter. The mean of the signals was subtracted before cross-correlation maximisation. The sample at which the cross-correlation had its maximum peak corresponded to the delay in samples and was used to shift the respiration rate either backwards or forwards in time.

As the predecessor of the new respiration algorithm tended to overestimate RR especially during AF, the interbeat interval (IBI) time was assessed, as this reflects the regularity of the heart rate. The standard deviation (SD) of the time in between two normal beats (SDNN) was calculated to assess regularity of the heart rhythm. In addition, results of the clinical ECGs were checked to confirm possible arrhythmia diagnosis.

Bland-Altman analysis

Bland-Altman Analysis for repeated measurements accounts for within-subject variation by correcting for the variance of differences between the average differences across patients and the number of measurements per patient[63]. Primary outcomes were bias and precision. The 95% limits of agreements (LoA) were calculated as ±1.96 SD of the difference. Respiration was considered to be acceptable for clinical purposes if it was estimated within ± 3 breaths/min of the reference monitor.

Clarke-Error Grid analysis

Clarke-Error Grid analysis was performed to evaluate consequences for clinical decision making [64]. A scatterplot in combination with a grid on top shows the relation between reference (VitalPatch) and index (Masimo Radius-7) measurement. Figure 4.6 depicts the CE grid, which is converted from a glucose grid [48]. Data-points within region A represent values within 20 % of the reference sensor, with the diagonal representing perfect agreement between both methods. Region B indicates small errors and values within C, D and E might be dangerous, as within these regions bradypnea is incorrectly assessed as tachypnoea or vice versa.

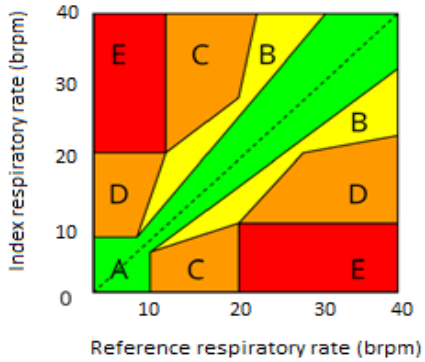

Figure 4.6 Clarke-Error Grid for comparison of index (VitalPatch) and reference (Masimo) respiration.

4.2.5 Analysis: Reliability of data transfer measured by the VitalPatch at home

Technical feasibility of home monitoring with the VitalPatch was assessed by the amount of data that was transferred. The percentage available data per hour was calculated, as was sent daily to the surgeon. Available data was defined as presence of HR, RR and skin temperature samples. As data from previous data gaps were uploaded later during the measurements, the percentage available data after the study was calculated as well and compared to the percentage available data during the study. The

amount of available data was considered sufficient if more than 70% of the data was available. Furthermore, the number of gaps within the available data after the study was calculated. A gap was defined as a period longer than 1 minute during which no data is transferred. Gaps were categorized in: 1-15 minutes, 15-30 minutes, 30-60 minutes, 1-4 hour and more than 4 hours. Moreover, reasons for data-gaps were searched for.

4.2.6 Analysis: Normal recovery pattern

The scores of concern assigned by the surgeon were compared to assess to what extent vital signs confirm or contradict the conclusion about the patient's condition based on the teleconsultation. In addition, they were used to determine what alarming vital signs are according to surgeons. All patients without adverse event at home were included to describe normal recovery pattern of EROES patients at home, in terms of HR, RR skin-temperature and activity. An adverse event was described as a complication identified by the surgeons that required intervention.

First of all, to evaluate the trend of vital signs, average values for HR, RR and skin temperature were calculated for each night (23:00-07:00), from 4 days before discharge until the 7th day at home. This analysis included all patients without adverse event and was performed on vital signs during the night, as circumstances are most similar and they are generally not influenced by activity. Besides the home recordings, the four days before discharge were included as well, to compare home and hospital setting.

Secondly, physical activity was assessed by the number of steps per day, which was calculated for patients individually and on average. Recordings were excluded in case of patch dislodgement.

Thirdly, the temporal pattern in vital signs was studied by analysing the probability density function of HR and RR on average of all patients without adverse event in the home recordings. Probability density functions of HR and RR were calculated for all seven days, and epochs during night (23:00-07:00) and daytime (07:00-23:00) were compared for all patients on average. Furthermore, to assess variation of HR, RR and skin temperature during the day, vital signs were averaged from 12:00 to 12:00 next day, for all seven days. Patients were included if no gaps larger than one day were present.

Lastly, HR and RR during periods of activity and inactivity were compared during the first seven days at home, to evaluate influence of activity and to assess changes over time. Every 15 minutes, epochs were labelled as 'inactive' (0-100 steps), 'moderately active' (100-300 steps) or 'active' (>300 steps). Probability density functions of all labels were compared during the first seven days at home for both HR and RR.

4.2.7 Analysis: Individual patterns

To evaluate the possibility for future use of the normal recovery pattern as a normative baseline, (cumulative) distributions of HR and RR of individual patients were compared with the distributions of all other patients. Two case examples were described. Kolmogorov-Smirnov (KS) metric and Bhattacharyya (Bhat) distance were used to compare the distributions[65]. KS (equation 5.1) quantifies the maximum distance between the cumulative distribution functions (CDFs) and Bhat distance (equation 5.2) measures the amount of overlap between two distributions. Both metrics converge to zero for identical distributions. Maximum for KS is 1, whereas maximum for Bhat distance is infinite.

$$\Delta KS\ (p, q) = \sup\left(|P(X) - Q(X)|\right) \qquad \text{equation (4.1)}$$

$$\Delta Bhat(p, q) = -\log\left[\sum_{x \in \mathrm{X}} \sqrt{p(x)q(x)}\right] \qquad \text{equation (4.2)}$$

4.3 Results

4.3.1 Patient demographics

From June to September 2019, 12 patients were asked to participate in the study, of which 10 gave informed consent for the home monitoring study (figure 4.7). Of these 12 patients, five were also asked for the validation measurements at the IMCU or general ward. Of these patients, two gave informed consent. In addition, one patient was included for the validation study that did not participate in the home monitoring study (yet). Patient demographics are summarized in table 4.1. Appendix E shows individual patient characteristics. All patients had at least one adverse event during hospital stay (table 4.2) and none of the patients developed an adverse event at home after discharge.

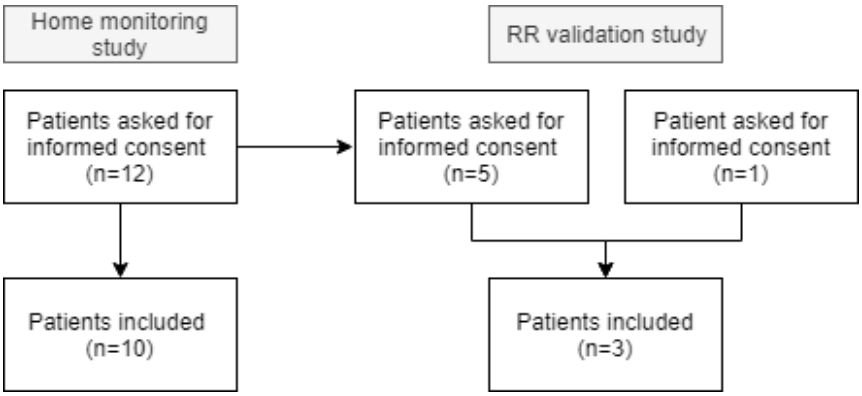

Figure 4.7 Flowchart of patient inclusion.

Table 4.1 Patient characteristics. BMI: body-mass-index. IQR: interquartile range.

		Number of patients
Age *median (IQR)*		67 (12)
Sex *n (%)*	Female	20
	Male	80
BMI (kg/m^2) *median (IQR)*		25.95 (2.5)
Length of stay *median (IQR)*		10 (5)
Readmission within 30 days *n (%)*		0 (0)
Adverse event during hospital stay *n (%)*		10 (100)
Adverse event at home (first seven days) *n (%)*		0 (0)

Table 4.2 Type and number of adverse events during hospital stay

Type of Adverse Event	**Number of patients**
Atrial fibrillation	4
Pneumonia	7
Anastomotic leak	4
Pneumothorax	1
Atelectasis	1
Spleen infarction	1
Chyle leak	1

5.3.2 Agreement and accuracy of the VitalPatch

In total 89 hours of simultaneous measurements with VitalPatch and Masimo Radius-7 (reference) were successfully recorded in three patients and used to assess agreement of RR (Figure 4.8).

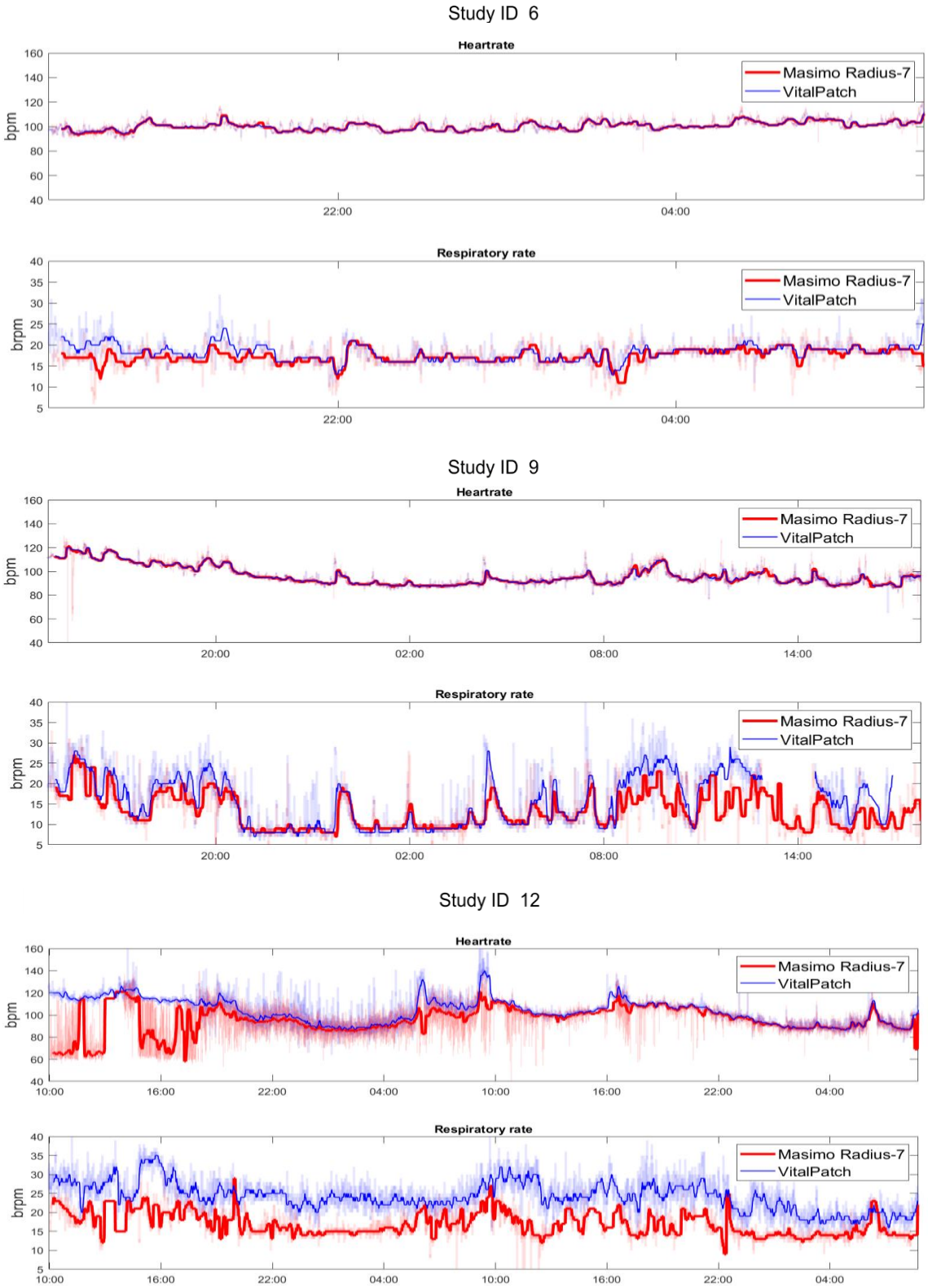

Figure 4.8 Continuous heart rate and respiratory rate measurement with both VitalPatch and Masimo Radius-7 of study ID 6,9 and 12. Median filtered signals are displayed in blue (VitalPatch) and red (Masimo Radius-7), and the unfiltered signals are displayed in light blue and pink respectively. Bpm: beats per minute, brpm: breaths per minute.

RR measured by the VitalPatch clearly followed reference RR for study ID 6 and 9. However, for study ID 12 RR was overestimated by the VitalPatch. For this patient, just before reference measurements were initiated ECG confirmed sinus tachycardia with supraventricular extrasystoles. Subsequently, AF with fast ventricular frequency and incomplete right bundle branch block was diagnosed the day after the reference measurements. SDNN of the recordings were 31, 55 and 115 milliseconds respectively, which confirmed irregular rhythm of the heart of study ID 12.

The Bland-Altman plot constructed from the validation recordings is shown in figure 4.9. Several observation pairs were located around a zero difference, but the majority was located below zero. VitalPatch overestimated RR with an average bias of -4.7 brpm and standard deviation of 4.7 brpm. Wide lower and upper 95% Limit of Agreement (LoA) of -13.9 and 4.6 brpm respectively were found. Appendix F shows bias and standard deviation for each study ID. For study ID 6 and 9 bias was substantially lower than for study ID 12. Result of the Clarke-Error Grid analysis is depicted in figure 4.9 as well. 43 % of the datapoints were located within region A, while region B included 57% of the datapoints. Individual Clark-Error Grid analysis is shown in appendix F.

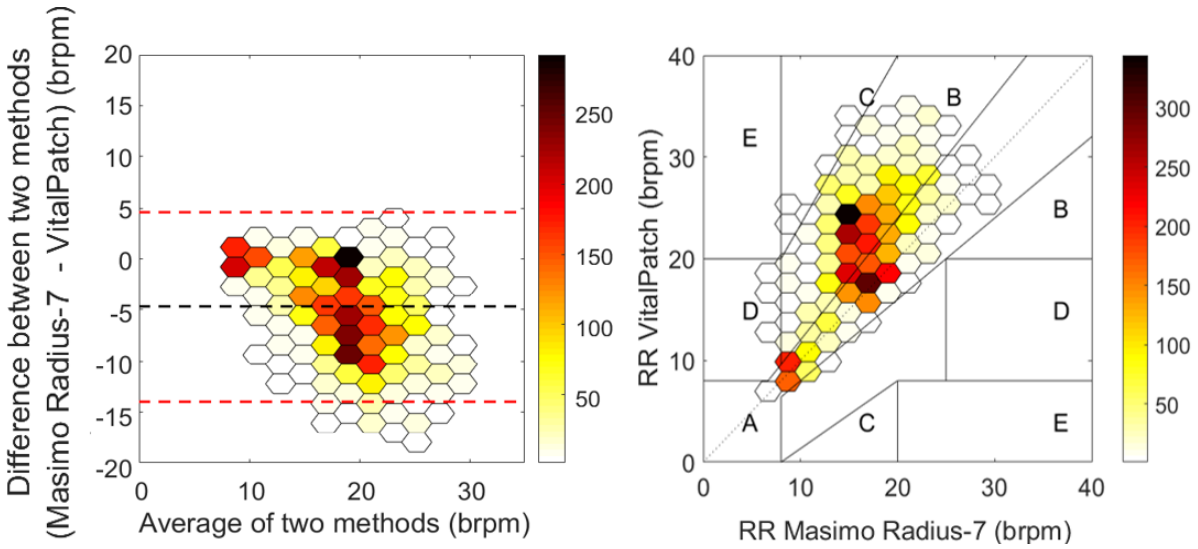

Figure 4.9 Left figure: Bland-Altman plot for the agreement in respiratory rate between the reference (Masimo Radius-7) and VitalPatch. Right figure: Clarke-Error Grid plot for respiratory rate, showing the relation between the reference (Masimo Radius-7) and VitalPatch.

4.3.3 Reliability of data transfer measured by the VitalPatch at home

Figure 4.10 shows the percentage of available data as provided daily to the surgeons. Notably, for three patients, several major data gaps were present during the study. For other patients there were some gaps as well, but most of the data were present. Several reasons for these data gaps were found. For one patient excessive sweating caused the patch to fell off several times. Another patient forgot to replace the patch, which resulted in a small data gap due to an empty battery. The other patch replacements were all successful. Other gaps were caused by either Bluetooth or internet connection failures. At first, even though patients were instructed to keep the phone within Bluetooth range, three patients forgot to take the phone into their bedroom during the first night, which resulted in Bluetooth disconnection. For two patients, unacceptably large data gaps were present, which we assumed were caused by failure of internet connection. Bluetooth connection between the patch and the phone was established and verified by the researcher (by means of a telephone call to the patient), but data were not transmitted to the server. One gap was caused by failure of automatic Bluetooth reconnection after re-attachment of the patch. Remainer data gaps were unexplained.

Table 4.3 shows the amount of available data during the study (as was sent to the surgeons daily) and after the measurement. For seven patients the amount of available data was above 70% during the study and after the measurement. If large data gaps were present during the study (on the daily vital signs printouts), the amount of available data after the end of the measurement period was considerably higher, since data was uploaded later during the measurement after re-establishment of Bluetooth and internet connection.

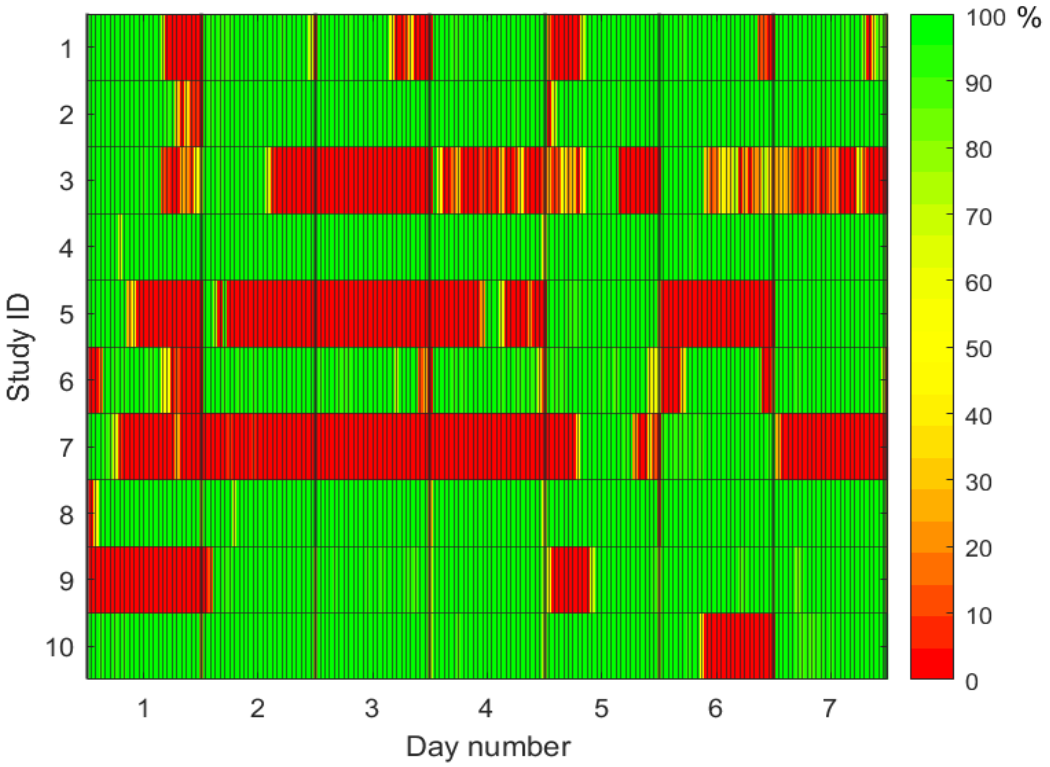

Figure 4.10 Percentage of available data per patient during the study, displayed for every hour.

Figure 4.11 shows the percentage of gaps within different categories. 83 % of the total number of gaps (267) were present for the three patients with least available data during the study and after the measurement. The median duration of all gaps was 9 minutes with an interquartile range of 31 minutes.

Table 4.3 Average amount of available data during the study and after the measurement per patient and on average.

Patient	Available data during study	Available data after measurement
1	80 %	99 %
2	95 %	99 %
3	35 %	55 %
4	98 %	100 %
5	37 %	52 %
6	83 %	94 %
7	25 %	33 %
8	96 %	100 %
9	77 %	88 %
10	88 %	99 %
Average	71 %	82 %

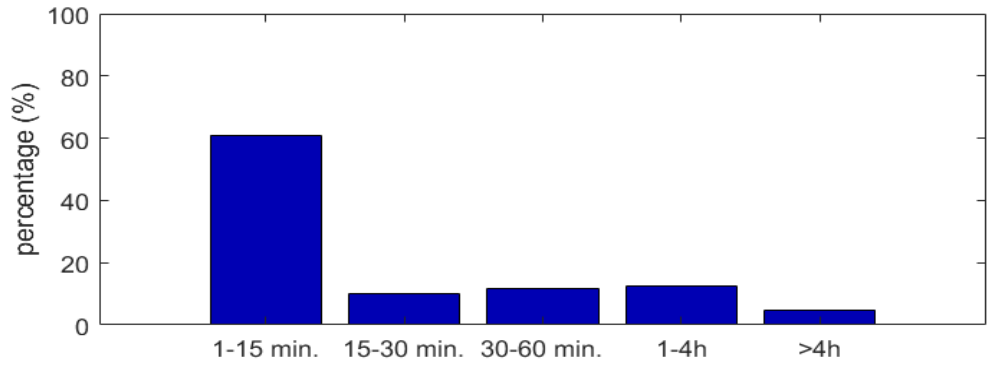

Figure 4.11 Gaps within available data after the measurement, presented in percentage of total number of gaps, within each category of all patients.

4.3.5 Normal recovery pattern

Scores of concern

All 'concern scores' after teleconsultation (TC) and after inspection of vital signs are shown in table 4.4. None of the included patients deteriorated at home, which corresponded with the scores of the surgeons as the surgeons assigned a score of 0 after both TC and inspection of vital signs in most cases. Twice, the surgeon assigned a score of 1 for both TC and vital signs. One patient had a resting HR of 100 and had troubles with his voice. The days after, HR stayed high and no increasing trends were present. Another patient mentioned that he felt feverish and the surgeon noted that he sounded slightly dyspnoeic during the teleconsultation. His resting HR was also around 100 and skin-temperature was 36 degrees. Later during the measurement, the skin-temperature was as high, but patient did not mention anything about fever.

Table 4.4' Score of concern' of all patients in the first seven days at home, after telephone consultation (TC) and after inspection of measured vital signs. X = impossible to assess, 0 = recovery in accordance with standard, 1=moderately worried, 2 seriously worried.

Patient number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Score after TC/Score after vital signs	**0/0**	6	5	5	6	4	7	4	7	6	7
	0/1	1	1	-	-	1	-	-	-	-	-
	0/X	-	-	1	-	2	-	3	-	1	-
	1/1	-	-		1	-	-	-	-	-	-

Since no AEs occurred during the home monitoring, vital signs of all included patients were considered to belong to a normal recovery pattern

Vital signs

Figure 4.12 depicts average HR, RR and skin temperature of all patients recorded before and after hospital discharge. Average decrease in HR was strongest from the second to the fifth day at home, where it decreased from 89 to 83 bpm. For RR, a subtle decrease was present. Contrarily, skin temperature increased slightly at home. It is notable that variation between patients is large.

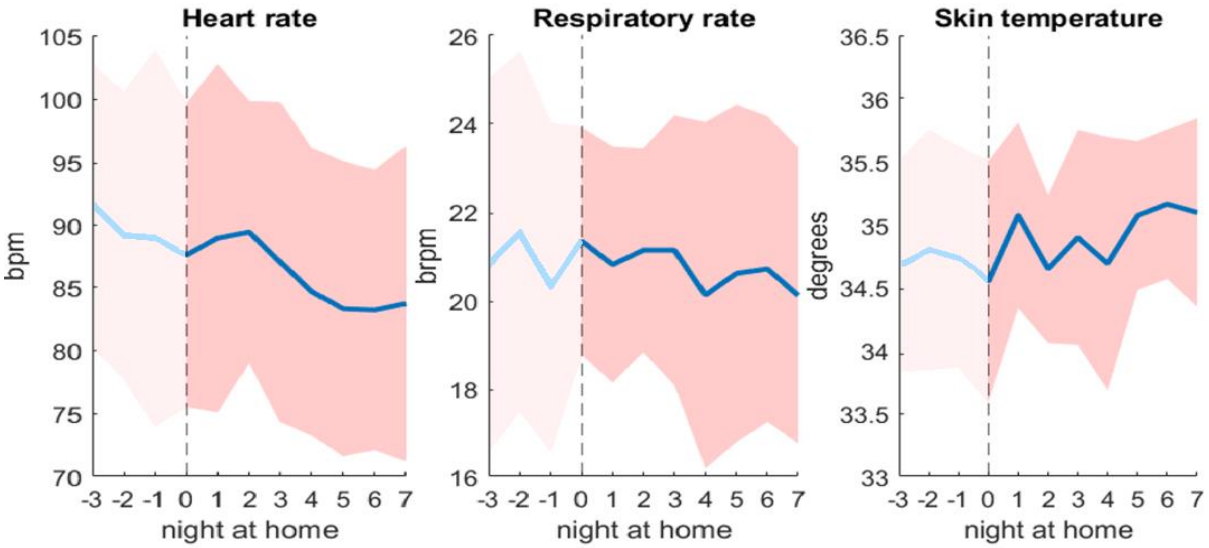

Figure 4.12 Average HR, RR and skin temperature of all patients in blue, with one standard deviation in pink. The vertical dotted black line indicates last night within hospital. Bpm: beats per minute, brpm: breaths per minute.

Day versus night

Figure 4.13 shows the average HR, RR and skin temperature during the day. HR showed a clear increase in the morning and afternoon and a decrease during the night. RR was also lower during the night, where it was on average 2 brpm lower. Skin temperature varied during the day as well and reached its maximum just before midnight. Over the night, skin temperature decreased and when waking up it started to increase again.

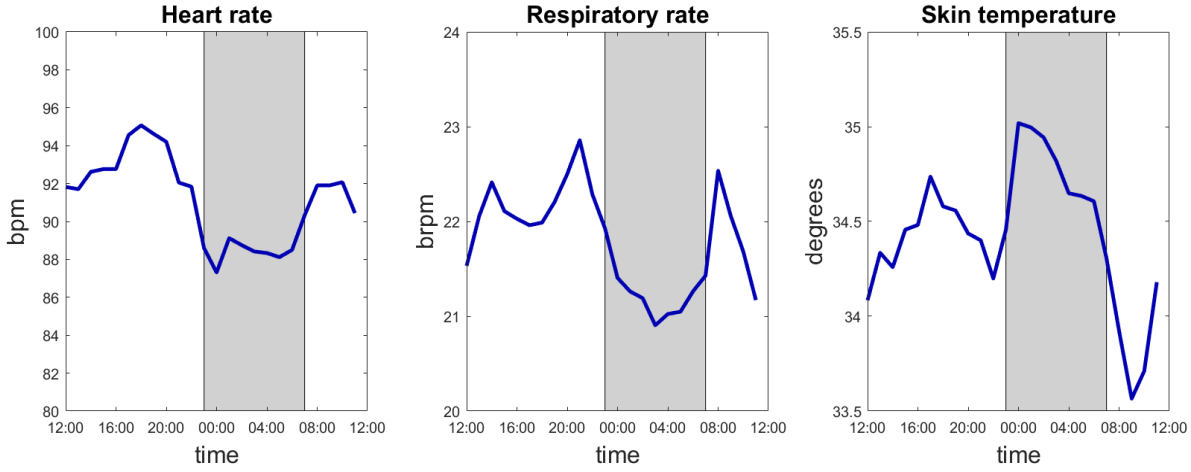

Figure 4.13 Circadian rhythm of heart rate, respiratory rate and skin temperature. The shaded area indicates nighttime. Bpm: beats per minute, brpm: breaths per minute.

Figure 4.14 shows the probability density functions of HR and RR of all patients during day and night in the first seven days at home. First, HR and RR showed a bimodal or multimodal distribution, except for RR during the day, which was normally distributed for all seven days. During daytime, median HR and RR were equal to or higher as compared to night-time. In the night recordings, maximum values for HR shifted downwards over time.

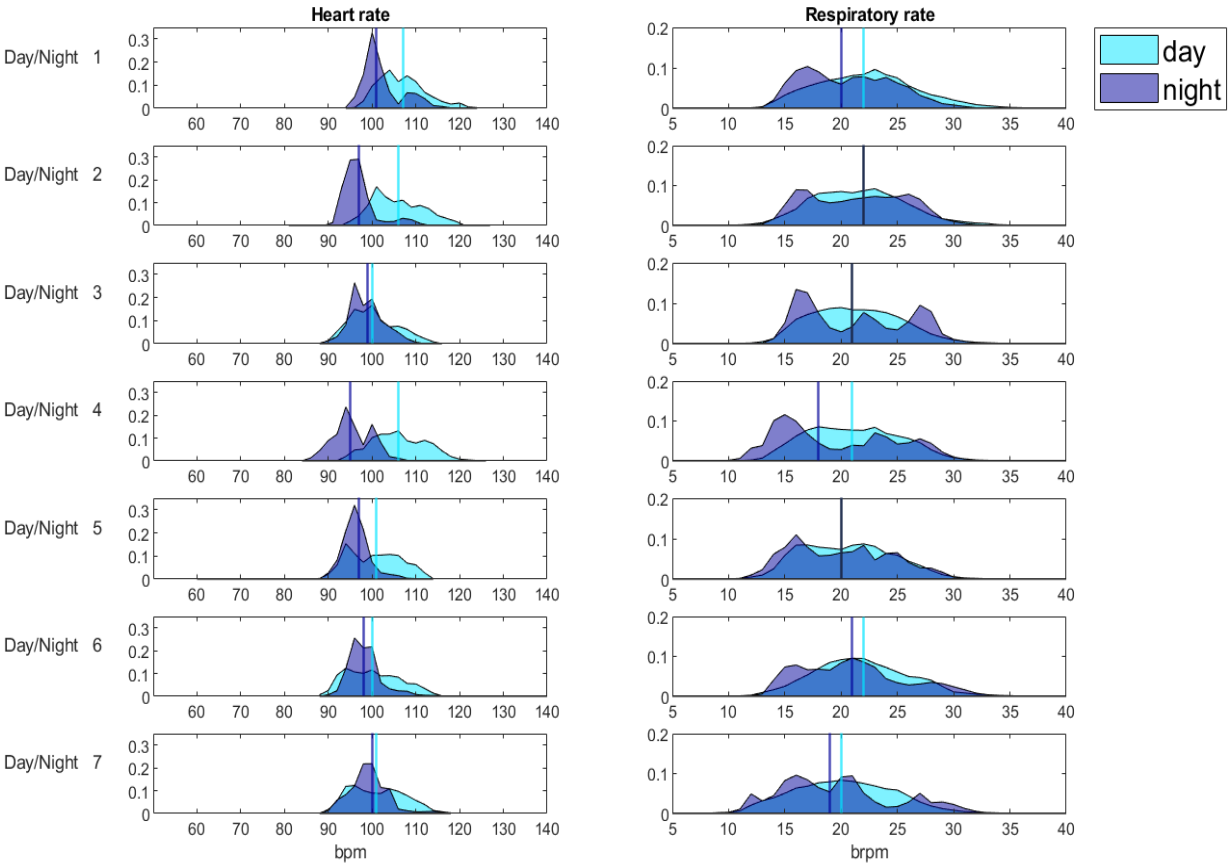

Figure 4.14 Probability density function of HR and RR of all patients, during night (23:00-07:00) and day (07:00-23:00). Median of each distribution is represented by the vertical line in its corresponding colour. If the median HR or RR during day and night were similar, the vertical line is displayed in grey.

Activity

Figure 4.15 shows the number of steps per day at home of all patients except patient 5, who was excluded in this analysis as patch dislodgement occurred. On average, a notable increase in activity over time was present. Appendix G shows the number of steps per patient. Variation between all patients was large. One patient barely walked during the first week after discharge, while two patients reached more than 3000 steps a day.

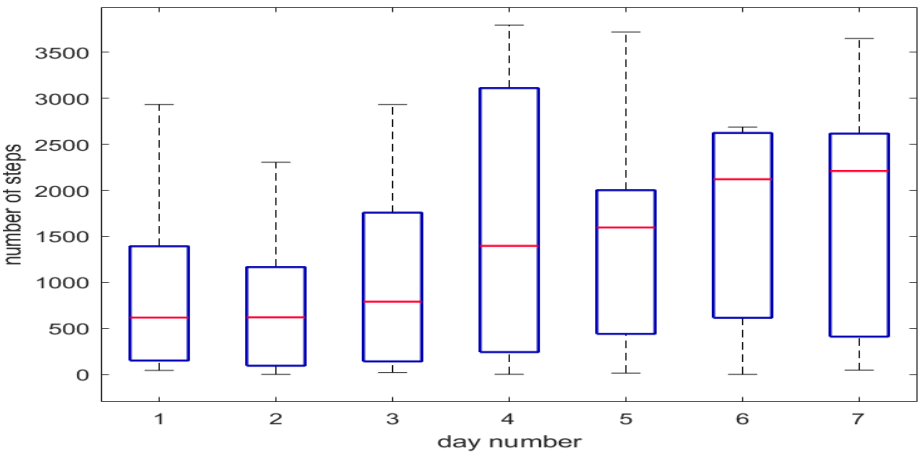

Figure 4.15 Box plot of the number of steps per day at home (N=9 patients). Red lines indicate median values, top and bottom edges of the blue box indicate 25th and 75th percentiles and the whiskers extend to the most extreme points.

Influence of activity on HR and RR

Figure 4.16 depicts probability density functions of HR and RR during inactive, moderately active and active periods. HR was clearly associated with activity, as the average HR was 10-15 bpm higher in presence of activity as compared to rest. Especially from the first to second day, a clear decrease in HR during activity was present. The difference in HR between moderate and high activity levels increased over the days, as it increased for high activity level. RR was more similar over time, but was also higher during activity. During the 6th day, RR was higher during moderately active periods, when compared to inactive and active periods.

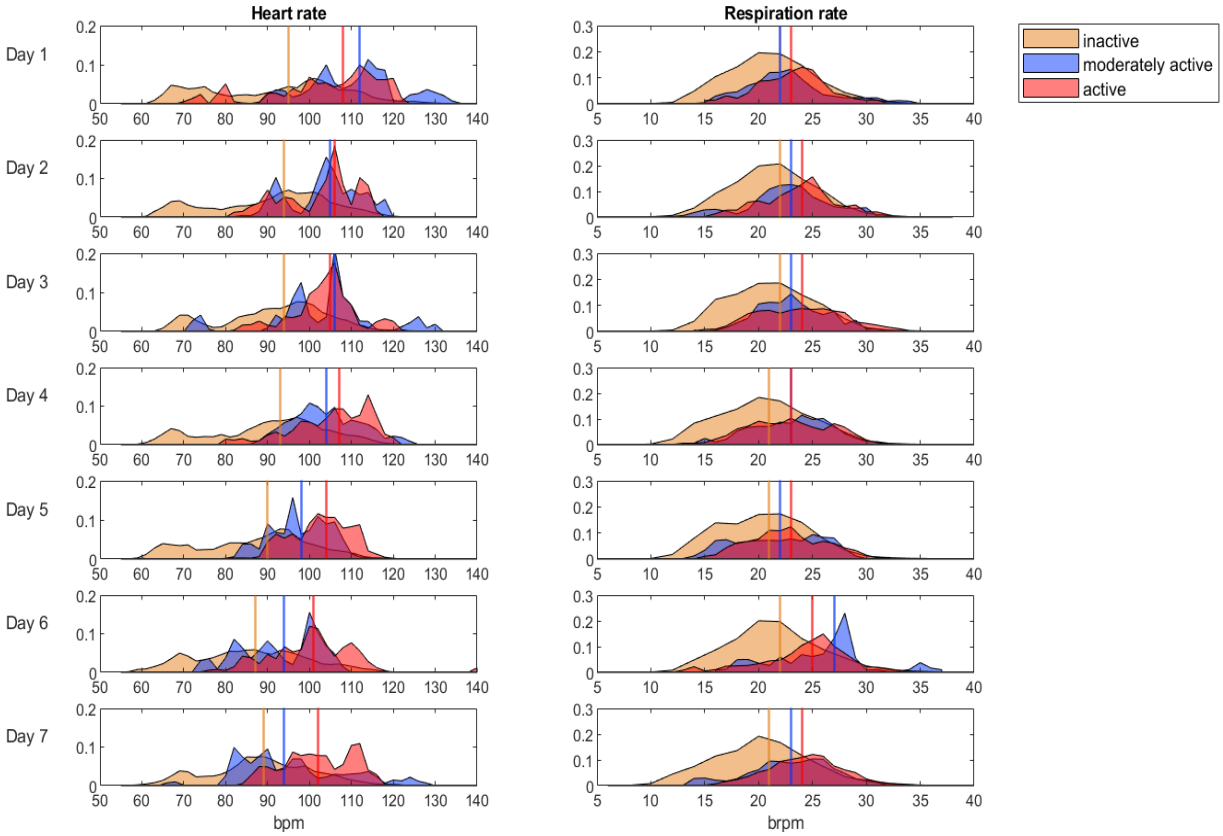

Figure 4.16 Probability density function of HR and RR of all patients while being inactive, moderately active and active. Median of each distribution is represented by the vertical line in its corresponding colour.

5.3.8 Exploring future possibilities: Bhat distance and KS distance case examples

Figure 4.17 shows first case example, where the distribution of HR and RR of study ID 6 was compared to the distribution function of all other patients. For this patient, who received beta blockers, HR and RR distributions were constant at home, and considerably lower than the group distribution. As the difference between these distributions and distribution of all other patients was quite high for both HR and RR, Bhat and KS distance were constantly high as well (figure 4.19).

Figure 4.18 shows the second case example, comparing HR and RR distributions of study ID 9 and the distribution of all other patients. Clearly, HR was high when compared to the other patients at the start of home monitoring and decreases during the first seven days, whereas RR showed no notable difference. Figure 4.19 depicts Bhat and KS distance, which shows a clear decrease over time for both metrics for HR, reflecting the downward shift of the distribution, whereas for RR they both fluctuated.

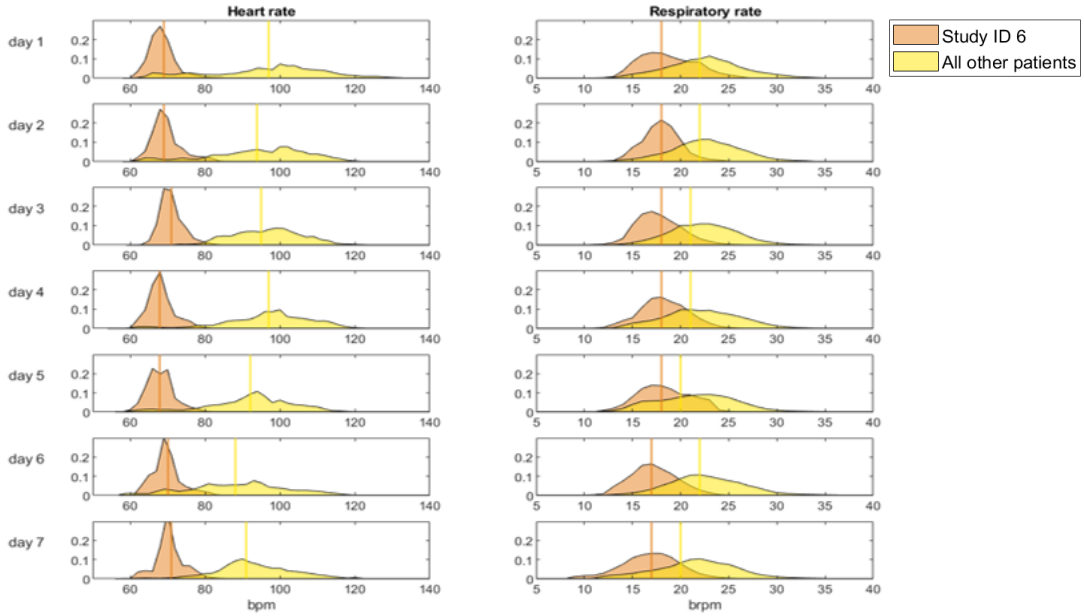

Figure 4.17 Probability density function of HR and RR for study ID 6, compared with the probability density function of HR and RR of all other patients. Bpm: beats per minute, brpm: breaths per minute.

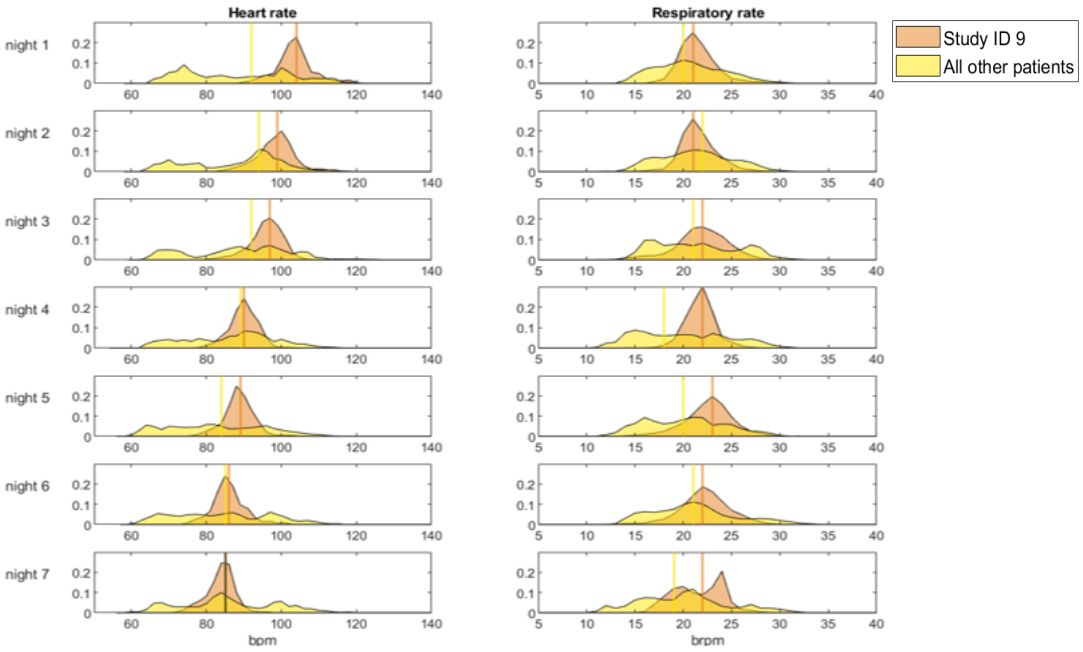

Figure 4.18 Probability density function of HR and RR for study ID 9, compared with the probability density function of HR and RR of all other patients. Bpm: beats per minute, brpm: breaths per minute.

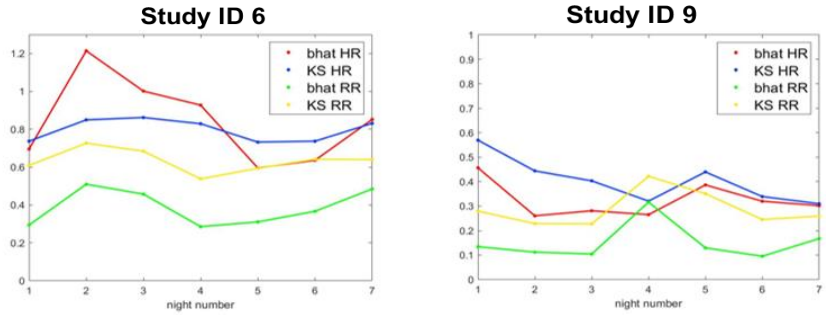

Figure 4.19 Bhat distance and KS distance between the probability density function of HR and RR of study ID 6 and 9 compared to the probability density function of all other patients.

4.4 Discussion

We studied the technical and clinical feasibility of continuous vital signs monitoring in high-risk surgery patients after discharge at home. The results show that it is feasible to remotely measure HR, RR, skin temperature and number of steps using the VitalPatch, since the amount of available data was sufficient to evaluate the vital sign trends of the last 24h for the majority of patients. Moreover, we were able to describe patterns of normal recovery at home, which can serve as a baseline for future home monitoring studies.

Technical feasibility of home monitoring

For 70% of the patients the amount of available data was above 70% for the daily vital sign assessment by the surgeons. Several unacceptable data gaps of more than one day were present in 30% of the patients. For these patients, the amount of available data after the measurement period was much higher when compared to as the available data as was daily assessed by the surgeons. Data from initial data gaps was uploaded later during the measurement or even afterwards. Several reasons for these data gaps were found.

The first cause of missing or delayed data were Bluetooth connection failures. If Bluetooth connection failed, data was saved onto the patch up to 18 hours. This data needed to be sent before the patch was empty or replaced. During the study the application did not automatically reconnect with the patch via Bluetooth after disconnection. This has been solved by an update of the application. Therefore, the percentage of available data during future studies is expected to be higher than within the current study.

A second reason for missing data was related to a poor internet connection at home. If no internet connection was available, the phone could store data up to 5 days. In case of missing data, it took up half of the time of the gap duration to re-upload this data to the server. Nevertheless, also after finishing the measurements, available amount of data was less than 70 % for three patients, which remains unexplained.

The researcher daily checked whether data was uploaded to the server. In case of failure, patients were called and asked to reboot the phone. Subsequently, the application automatically reconnected with the patch and new 3G connection was set-up. This often resolved the connection failure problems.

Recovery pattern

A normal recovery pattern of EROES patients in terms of vital signs and activity was described. Even though the number of widely varied between all patients, a clear increase was present during the first seven days at home. Alongside, average HR and RR decreased over time. Circadian rhythm of HR, RR and skin temperature followed a similar pattern though showed less variation when compared to healthy subjects[38][40]. Differences between individual patients were quite high. For some patients, difference between day and night was large, whereas for others this was barely present. This could be explained by inactivity during the day or the recovery process. Some patients slept in the afternoon, which probably affected the average circadian rhythm. Moreover, HR and RR distributions of all patients during the day and night were compared. Both HR and RR showed lower distribution during the night. HR during both day and night decreased during the first days at home. A slightly higher HR was found during the last day, which is expected to be caused by the higher number of steps taken at the seventh day.

Besides day and night differences over time, the influence of different activity levels was studied. As expected, HR and RR were higher during moderately active and active periods when compared to

periods of rest. Differences for HR were larger than for RR. In some cases, HR or RR was equal to or higher for moderately active periods when compared to active periods, which was probably caused by a different number of epochs in each category for different patients.

A normal recovery pattern at home was described using data from all patients, as none of them required intervention after discharge. Nevertheless, these patients showed individual differences. At first, the moment of discharge differed per patient. For example, one patient was allowed to be discharged home one week before official discharge, as homecare was not arranged yet. Therefore, this patient might have been further in the recovery process than others. In addition, all patients have suffered from one or more adverse events within hospital, of which severity differed to a great extent. This influences the vital signs measured at home.

Different types of patients can be distinguished. Three patients were discharged home with a high resting HR of about 100, which continued to be high at home. A high resting HR that decreased slightly at home was present for three other patients. One patient showed a strong decrease in resting HR. Lastly, there were three patients with a low resting HR at discharge, which continued to be low, as these patients received betablockers. This emphasizes the difficulty to describe a general normal recovery pattern, as individual differences are large. It is therefore important to compare the vital signs of a patients with previous measured values for that particular patient, as trend information improves prediction of clinical deterioration [19]. Therefore, it is relevant to start the vital signs recording within hospital before discharge, to allow comparison of vital signs over time. Even though individual differences were present, the described recovery pattern in the current study is relevant as it can be used for comparison with future discharged patients. It was impossible to correct for individual effects due to the limited number of included patients. Since individual differences will also occur in future, the population in the current study probably covers future populations too.

The initial plan was to calculate KS and Bhat distance [65] between distributions a patient that deteriorated at home and all patients with normal recovery, to evaluate whether and to what extent these patients deviated from a normal distribution. Relevant information is obtained if both metrics increase over time, which is not caused by a downward shift of the distribution when compared to all other patients. As no adverse event occurred during the home monitoring, two case examples of patients without adverse event were described, to evaluate possibilities for future use. Both metrics were large for HR and RR even though low resting HR and RR were present in the first example. So, these metrics only express distance between two distributions, but do not tell whether the distribution was higher or lower than the distribution which with it was compared to. Moreover, high metrics were generally found, as the range of the distributions of patients with normal recovery was wide. This emphasizes the relevance of studying differences within patients and to visually compare it with previous days. These metrics seemed more useful for HR when compared to RR, as the accuracy which with RR is measured is smaller compared to variation during the day and or an underlying complication. Pimentel et al. studied the physiological trajectory of patients at the upper gastro-intestinal ward by means of KS and Bhat distance. They showed that the difference in distributions for RR were bigger than for HR, when comparing with the last day before discharge. This may be explained, as they used manual measurements instead of continuous monitoring, which were shown to have different results[34].

Agreement of respiration measurement

Measurements with the reference monitor showed that RR was overestimated with 4.7 brpm by the VitalPatch, which is above the acceptable limit. VitalConnect showed a mean absolute error of 3.3 brpm [62]. However, this was during both stationary and ADL tests in healthy subjects. Breteler et al. showed a mean absolute error of 2.4 brpm using the predecessor of the VitalPatch in high-risk

patients[48]. Within the current study the number of patients was limited and therefore we are not able to conclude about improvements of the RR algorithm as compared to its predecessor. Although, for patients without AF, RR measured by VitalPatch followed RR measured by the reference device very closely. Therefore, influence of outliers by the reference device were expected to be minimal. For the patient with irregular heart rhythm, RR was overestimated at unacceptable level. As AF is not uncommon in EROES and other high-risk patients this is relevant to take into account[66]. For future use, a warning about possible uncertainty of RR during irregular heart rhythms could be useful, which could be based on a SDNN threshold.

Limitations and future perspectives

Before implementation of home monitoring, improvements are needed to prevent unacceptably large data gaps. At first, it is desired to have a patch that measures as long as the required monitoring period, to prevent data loss due to an empty battery. Future research needs to reveal optimal monitoring length. Furthermore, patients might forget to take the phone with them into the bedroom. It is desired to minimize the interaction between patient and the monitoring technique, since this may result in data gaps. For example, a smartwatch instead of a phone can be used. However, this requires patients to remember to charge the watch, which is not ideal either. Bluetooth 5.0, available in near future, could resolve the Bluetooth connection problem within or close to the house, as the range is four times bigger than currently used Bluetooth version (4.2)[67]. Bluetooth connection problems can be bypassed by using an Internet of Things (IoT) sensor, since data is then directly uploaded to the cloud. However, gaps due to internet connection failure might still occur. Instead of SIM card with 3G, Wi-Fi can be used to improve internet connection strength. This, however, requires patients to set-up this connection, which could be complicated for older patients. Connection problems with both Bluetooth and internet were often solved by restarting the phone. This required the researcher to check whether data was uploaded to the server. If this was not the case, the patient was called to find a solution. In the future, an automatic alert could be sent to a nurse if no data is uploaded for more than one hour. Within the current study, it took up to half of the time of the duration of the gap to upload the previously measured data. This greatly affected the amount of data that was sent to the surgeons daily. If a large data gap is present, it is recommended to not upload all previously measured data but for example one sample per five minutes. In this way, troubles with sending enormous amounts of data using a weak internet connection are prevented.

Within the current study, step count was not validated. The Biosensor, having the same hardware as the VitalPatch, detected walking accurately above 2.5 km/h [68]. It is expected that patients (after high risk surgery) often walk slowly, which would not be detected. This has possibly led to underestimation of activity. Therefore, in the future, raw accelerometer data can be used to define different levels of activity. The integrated modulus of the raw accelerometer data could provide better understanding of the context of the vital signs [68].

It is advised to retrieve more continuous vital signs data during future home monitoring studies. Subsequently, different types of patients can be distinguished, and patterns can described more specifically, which makes comparison of distributions more valuable. When these different types of patients are identified it may be more useful to use metrics such as Bhat and KS distance. The current study focussed on the distribution of HR and RR individually. To provide a deeper insight, the joint probability of HR and RR can be studied.

Since no patient deteriorated at home, it is still unknown whether this would have been detected on time using remote monitoring of vital signs, that were inspected once a day. Although, it was not the aim of the current study to prove added value of home monitoring, but to determine feasibility and to

describe a normal recovery pattern. This can serve as a baseline for future studies, that need to be performed to assess added value of home monitoring in high-risk patients.

4.5 Conclusion

It is feasible to remotely measure HR, RR, skin temperature and number of steps using the VitalPatch in the first week after discharge at home, since for the majority of patients the amount of available data was sufficient to evaluate the vital sign trends of the last 24h. For 70% the amount of available data was above 70% and for 30% of the patients several unacceptably large data gaps were present. Patterns of normal recovery at home were described, where clear differences were found between day and night, and active and inactive epochs. For future home monitoring, these patterns can be used for comparison of vital signs of a new patient. More continuous vital signs data of patients after high-risk surgery after discharge at home needs to be retrieved, to study possibility of detection of clinical deterioration at home.

Chapter 5: Final Discussion

Even though several technical applications for continuous vital signs monitoring are available, such systems are not implemented at the general ward or remotely at home. Beforehand, several aspects need to be considered, of which some were studied within this thesis.

At first technical and clinical feasibility of continuous (home) monitoring needs to be assessed. Thereafter, a plan for implementation within the workflow of current (hospital) care is required. As it is undesired to have many false alarms, an adequate alarming system is required. Wireless monitoring aims to facilitate early detection of clinical deterioration, either within hospital or at home. Continuous monitoring also results in additional costs, as a nurse or surgeon is responsible for interpreting these vital signs. Therefore, cost-effectiveness studies need to be performed before implementation within standard care.

Within this thesis, relevant aspects of continuous home monitoring were considered. Even though both studies use continuous measurements of vital signs with comparable devices, each study was at a different stage of research. In contrast to the home setting, more data is available for analysis and development of algorithms at the general ward.

The first study showed possibilities of adverse event detection at the general ward using a new warning score that includes trend information, based on continuous monitoring with different wearable wireless sensors. The prediction algorithm should be further improved. Overfitting of the algorithm on the limited data should be avoided. Therefore more continuous vital signs data of high-risk patients at the general ward need to be collected. Statistical analysis on larger data sets are necessary to prove added clinical value. Moreover, observational studies to collect data of a broad range of high-risk patients including events are required to further optimize detection algorithms. Too early implementation in clinical setting might be hampered by the high level of false alarms, which need to be prevented.

Possibly the most challenging aspect in the development of prediction algorithms is labelling the adverse event offset. The registration of events depends on the timing of the nurse recording a diagnostic test in the EHR, which may be delayed. Ideally, a researcher should observe all monitored patients closely. All findings of doctors and nurses need to be documented consequently to be able to define the exact moment of onset of adverse event.

Even if this problem is tackled during future studies, other challenges remain. We have shown that patients with a normal recovery may also show trends in their vital signs. Furthermore, not all adverse events result in vital sign changes. For example, an X-ray can confirm a pneumonia, but this may not affect vital signs yet. Moreover, the overall condition (i.e., patients wellbeing) of the patients above vital signs only, is important. Therefore, it is important to compare a patient's condition with previous hours or days. This emphasizes the relevance of the standard nurse round. Nurse worry is something relevant which cannot be measured by devices. Therefore, we may conclude that continuous monitoring techniques can be used as a complement to standard care, instead of replacing it.

The second study that was performed for this thesis assessed technical and clinical feasibility of home monitoring of high-risk patients after discharge. An important difference between continuous

monitoring at the general ward or at home is that we lack context of the vital signs at home, as it is unknown what the patient is doing, how he looks and how he feels. Within hospital, a nurse can quickly check whether an alarm was false or not. At home we only have number of steps that were taken. In case of alarming vital signs the patient needs to be called. Nurses specialised in remote monitoring could check all monitored patients at home and call the patient when necessary. Another difference between continuous home monitoring and continuous monitoring at the general ward, is the risk of complications at home, which is considerably lower at home. Therefore, alarm strategies that need to be developed for home monitoring in future, may learn from algorithms that are used within hospital, but with its own conditions and constraints.

In contrast to continuous monitoring at the general ward, continuous home monitoring has not reached the stage of development of algorithms for clinical deterioration yet. First it was necessary to study technical feasibility. This study showed feasibility of continuous remote measurement with the VitalPatch, but also revealed the challenges of Bluetooth and internet connection failure.

In current practice, EROES patients generally have a consultation within hospital one week after discharge. Within the current study, enormous amounts of extra data were available. It was unknown what a normal pattern was in terms of vital signs and activity in the week after discharge at home. The described normal recovery pattern encompassed all patients without adverse event in terms of vital signs and activity, which widely ranged between patients. For example Initially it seemed worrying that a patient had a resting HR of 100 at home. However, apparently this was not aberrant for this patient, as it continued to be high during the study, while no adverse event occurred. This emphasizes the difficulties of describing a normal recovery pattern for different types of patients. The described patterns, however, will be useful to compare with during future home monitoring of EROES patients. As the currently available amount of data is insufficient to distinguish different types of patients, it is important to gather more data.

The future purpose of home monitoring is to facilitate early detection of deterioration, but possibly it may also be used to discharge patients one or two days earlier with extra surveillance. Before we are able to discharge patients earlier, the way of providing care needs to be reorganized. EROES patients are already discharged home early within 8 days instead of 16 days which was the norm in the UMCU recently. When further shortening the hospital stay, additional home care needs to be organized to assist in activities of daily living and physiotherapy. So, instead of focussing on technical aspects of remote monitoring of vital signs only, this needs focus as well. Eventually, cost-effectiveness studies need to be performed. This emphasizes the necessity of continuation of home monitoring studies to gather more data before it is implemented in clinical practice.

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Appendix A: VitalPatch

The VitalPatch is a wireless and wearable patch sensor that measures single-lead ECG, HR, interbeat interval (IBI) time, RR, skin temperature, body posture and step count. The VitalPatch needs to be placed on the left pectoral muscle, at a 45˚ angle and has a battery life of 120 hours [61][48]. The patch contains two ECG electrodes with hydrogel, a thermistor and a zinc-air cell battery. The sensor includes a tri-axial accelerometer and Bluetooth Low-Energy (BLE) transceiver for wireless connection with a relay device. HR is derived from the single lead ECG, measured in µV with a sampling rate of 125 Hz. A wavelet transform algorithm is used to detect the QRS-complexes. The R-R interval is the time within two consecutive QRS complexes. Subsequently, HR is determined by the reciprocal of R-R interval, averaged over 10 beats. Respiration rate is derived using a combination of different features. It combines accelerometer data with two ECG derived features: respiratory sinus arrhythmia (RSA) and amplitude modulation. The accelerometer data measures minimal movement of the chest wall during respiration. RSA is the variability in HR, in synchrony with respiration. The length of the R-R interval is shortened during inspiration and prolonged during expiration [53]. Amplitude modulation is caused by a change in cardiac axis with respect to the chest wall, caused by respiration, resulting in a variation in the QRS amplitudes. The average RR for all three respiratory signals is calculated during a 45-second window. Each of the three rates are calculated by excluding the top and bottom 10% of the individual rate. The total estimation of the respiration rate is a weighted average of the individual rates[61]. HR and RR have a sample frequency of 0.25 Hz.

Appendix B: MediBioSense platform

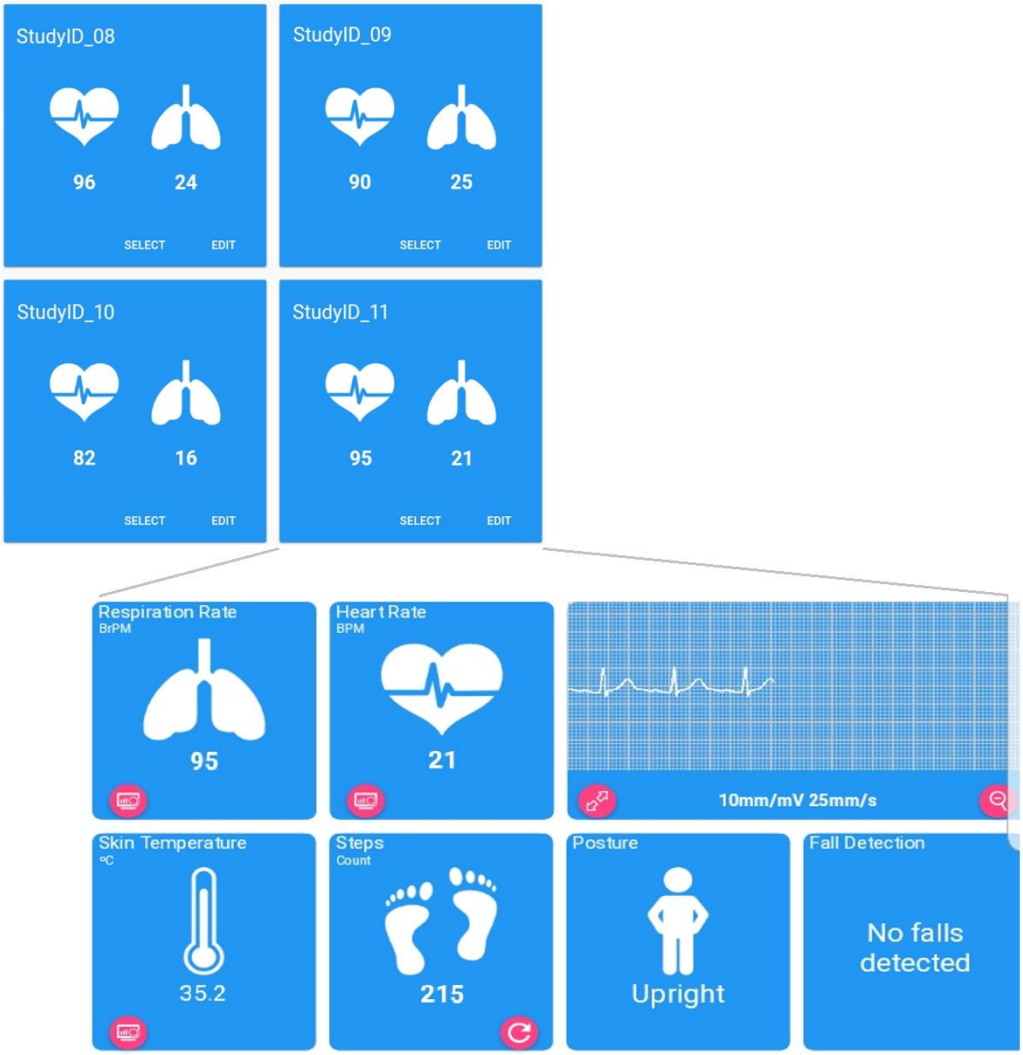
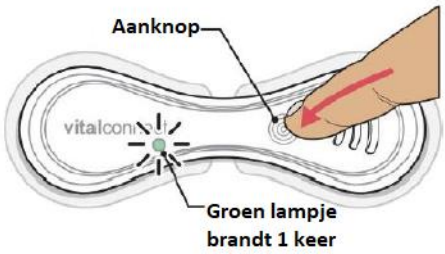


Figure B.1 Vital signs platform of MediBioSense, showing live data. The upper part of the figure shows an overview of all measurements. The lower part of the figure shows the detailed information, when selecting a specific patient.

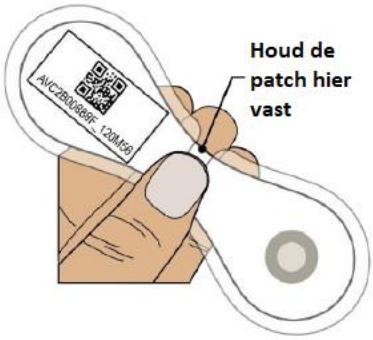
Appendix C: Instructions to replace VitalPatch (Provided in Dutch)

Hieronder volgt het stappenplan voor het aanbrengen van een nieuwe pleister:

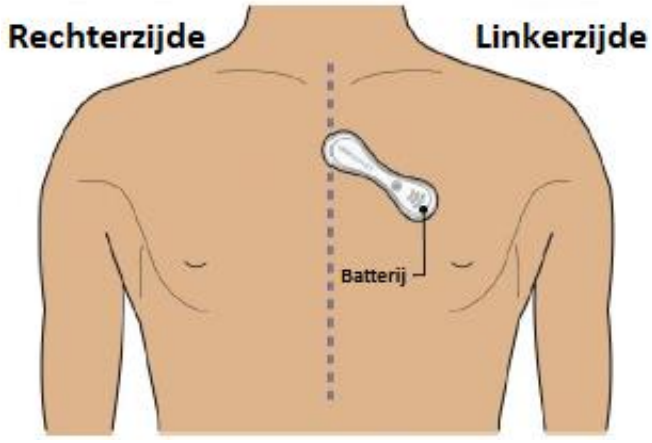
1. Haal de huidige pleister van uw borst.
2. Zorg ervoor dat uw handen schoon en droog zijn voordat u de nieuwe pleister aanbrengt
3. Verwijder indien aanwezig lichaamshaar op de plek van de pleister. Maak de huid ter plaatse van de pleister schoon met een alcohol doekje. Wacht vervolgens 2 minuten totdat de huid helemaal droog is.
4. Druk 3 seconden op de aan-knop, weergegeven in de figuur hieronder. Er zal eenmalig een groen lampje knipperen



5. Houd vervolgens de pleister in het midden vast, zoals hieronder weergegeven. Verwijder de doorzichtige folie aan beide zijden van de pleister.



6. U kunt nu de pleister aanbrengen. Let erop, dat de pleister niet op de kop zit. De tekst moet leesbaar zijn (VitalConnect). Druk de pleister stevig aan zodat deze goed vast zit. Het is belangrijk dat de pleister op de linkerzijde van uw borst geplakt wordt zoals in de figuur hieronder. Let op, de figuur hieronder is een vooraanzicht.



Appendix D: Patient diary (Provided in Dutch)

Tijdstip	Slapen	Rust	Matig actief	Actief	Omschrijving activiteit
00:00-01:00					
01:00-02:00					
02:00-03:00					
03:00-04:00					
04:00-05:00					
05:00-06:00					
06:00-07:00					
07:00-08:00					
08:00-09:00					
09:00-10:00					
10:00-11:00					
11:00-12:00					
12:00-13:00					
13:00-14:00					
14:00-15:00					
15:00-16:00					
16:00-17:00					
17:00-18:00					
18:00-19:00					
19:00-20:00					
21:00-22:00					
22:00-23:00					
23:00-23:59					

Hoe voelde u zich vandaag (omcirkelen)? 0 1 2 3 4 5 6 7 8 9 10

Toelichting:

Bijzonderheden met de sensor:

Appendix E: Patient characteristics

*Table E.1 Patient characteristics. * not measured/reported during pre-operative screening*

Patient	**Gender** (M/F)	**Age** (years)	**BMI** (kg/m^2)	**Length of hospital stay** (days)	**HR before** surgery (bpm)	**RR before surgery** (brpm)	**Adverse Event during hospital stay**
1	F	52	27	11	108	14	Pneumonia
2	M	68	25	9	100	16	Pneumonia
3	M	70	24	8	102	14	Atrial fibrillation
4	M	64	25	10	97	14	Pneumothorax, pneumonia
5	F	58	25	8	100	12	Pneumonia
6	M	69	28	21	70	13	Atelectasis, spleen infarction, anastomotic leak, atrial fibrillation
7	M	71	30	8	76	12	Atrial fibrillation
8	M	72	27	18	83	16	Chyle leak, anastomotic leak, pneumonia
9	M	56	25	13	-*	18	Pneumonia, anastomotic leak
10	M	66	27	9	73	14	Atrial fibrillation, pneumonia

Appendix F: Clark-Error Grid and individual Bland-Altman analysis

Table F.1 Bland-Altman analysis of respiration measured by VitalPatch, versus respiration measured by Masimo Radius-7. SD: standard deviation, LoA: limit of agreement.

Patient	Number of measurement pairs	Bias	SD	Lower 95% LoA	Upper 95% LoA
6	924	-0.8	1.6	-4.0	2.4
9	1458	-2.3	3.4	-9.1	4.5
12	2799	-7.2	3.3	-13.1	-0.7
6,9 and 12	5181	-4.7	4.7	-13.9	4.6

Table F.2 Percentages of data points located within region A, B, C, D or E for respiration measured by VitalPatch compared with the reference (Masimo Radius-7).

Region	Patient 6	Patient 9	Patient 12	Patient 6,9 and 12
A	94 %	69 %	12 %	43 %
B	6 %	30 %	88 %	57 %
C	0 %	0 %	0 %	0 %
D	0 %	1 %	0 %	0 %
E	0 %	0 %	0 %	0 %

Appendix G: Number of steps at home

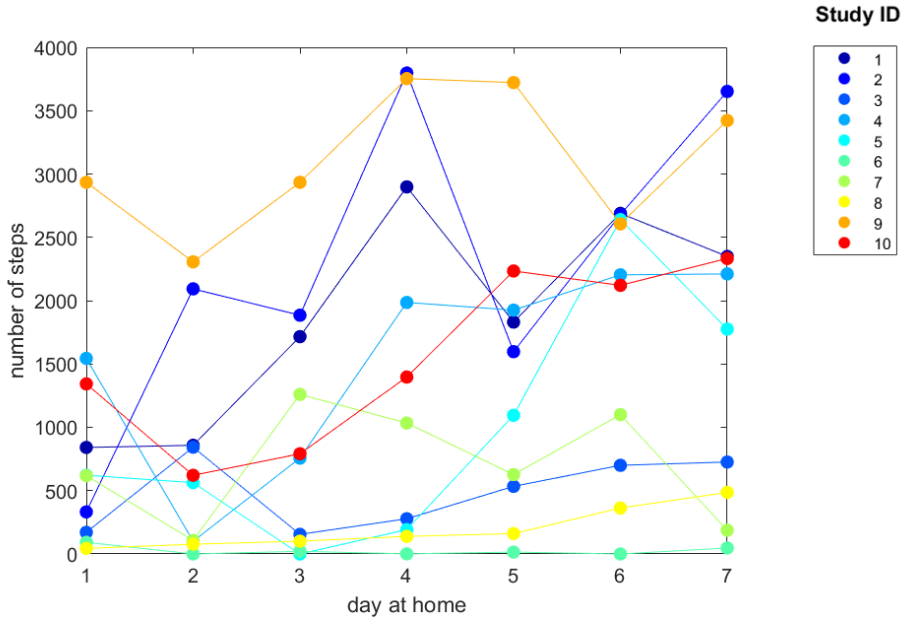


Figure G.1 Number of steps per patient first seven days after discharge