DOCTOR OF PHILOSOPHY

Wearable continuous vital sign monitoring for deterioration detection and clinical outcomes in hospitalised patients

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PhD

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Critical Overview Document: a Portfolio of Published Articles submitted to the Department of Intelligent Healthcare, Coventry University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy (PhD).

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Abstract

Current practice uses physiological early warning scoring (EWS) systems to monitor "standard" vital signs, including heart rate (HR), respiratory rate (RR), blood pressure (BP), oxygen saturations (SpO2) and temperature, coupled with a graded response such as referral for a senior review or increasing monitoring frequency. Early detection of the deteriorating patient is a known challenge within hospital environments, as EWS is dependent on correct frequency of physiological observations tailored to specific patient needs, that can be time consuming for healthcare professionals, resulting in missed or incomplete observations. Wearable monitoring systems (WMS) may bring the potential to fill the gap in vital sign monitoring between traditional intermittent manual measurements and continuous automatic monitoring. However, evidence on the feasibility and impact of WMS implementation remains scarce. The virtual High Dependency Unit (vHDU) project was designed to develop and test the feasibility of deploying a WMS system in the hospital ward environment.

This doctoral work aims to critically analyse the roadmap work of the vHDU project, containing ten publications distributed throughout 7 chapters. Chapter 1 (with 3 publications) includes a systematic review and meta-analysis identifying the lack of statistical evidence of the impact of WMS in early deterioration detection and associated clinical outcomes, highlighting the need for high-quality randomised controlled trials (RCTs). It also supports the use of WMS as a complement, and not a substitute, for standard and direct care. Chapter 2 explores clinical staff and patient perceptions of current vital sign monitoring practices, as well as their early thoughts on the use of WMS in the hospital environment through a qualitative interview study. WMS were seen positively by both clinical and patient groups as a potential tool to bridge the gap between manual observations and the traditional wired continuous automatic systems, as long as it does not add more noise to the wards nor replaces direct contact from the clinical staff. In chapter 3, the wearability of 7 commercially available wearables (monitoring HR, RR and SpO2) was assessed, advocating for the use of pulse oximeters without a fingertip probe and a small chest patch to improve worn times from the patients. Out of these, five devices were submitted to measurement accuracy testing (chapter 4, with 3 publications) under movement and controlled hypoxaemia, resulting in the validation of a chest patch (monitoring HR and RR) and proving the diagnostic accuracy of 3 pulse oximeters (monitoring pulse rate, PR and SpO2) under test. These results were timely for the final selection of the devices to be integrated in our WMS, namely vHDU system, explored in chapter 5, outlining the process for its development and rapid deployment in COVID-19 isolation wards in our local hospital during the pandemic.

This work is now converging in the design of a feasibility RCT to test the impact of the vHDU system (now augmented with blood pressure and temperature monitoring, completing all 5 vital signs) versus

standard care in an unbiased environment (chapter 6). This will also ascertain the feasibility for a multicentre RCT, that may in the future, contribute with the much-needed statistical evidence to my systematic review and meta-analysis research question, highlighted in chapter 1. Finally, chapter 7 includes a critical reflection of the vHDU project and overall doctoral work, as well as its contributions to the field of wearable monitoring.

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This thesis is dedicated to my Grandfather Francisco Morgado and Grandmother Idalina Laranjeira.

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Abbreviations

ABG	Arterial Blood Gas
AHP	Allied Health Professions
ANOVA	Analysis of Variance
ANSI/AAMI	American National Standards Institute/Association for the Advancement of Medical Instrumentation
BLE	Bluetooth Low Energy
BMC	BioMed Central
BMJ	British Medical Journal
BP	Blood Pressure
bpm	beats per minute
BST	British Summer Time
BRC	Biomedical Research Centre
CAG	Confidentiality Advisory Group
CCRG	Critical Care Research Group
CI	Confidence Interval
COVID-19	Coronavirus disease
ECG	Electrocardiography
EPR	Electronic Patient Record
EWS	Early Warning Score
GMT	Greenwich Meant Time
HR	Heart Rate
IBME	Institute of Biomedical Engineering
ICU	Intensive Care Unit
ISO	International Organization for Standardization
JMIR	Journal of Medical Internet Research
LoA	Limits of Agreement
LOS	Length of Stay
MAE	Mean Absolute Error
MCA	Mental Capacity Act
NIHR	National Institute for Health and Care Research
PPE	Personal Protective Equipment
PR	Pulse Rate

RCT	Randomised Controlled Trial
RMSE	Root Mean Square Error
rpm	respirations per minute
RR	Respiratory Rate
SaO2	Arterial Blood Oxygen Saturation
SEND	System for Electronic Notification and Documentation
SpO2	Peripheral Blood Oxygen Saturation
STS	Sit to Stand
UK	United Kingdom
vHDU	virtual High Dependency Unit
WMS	Wearable Monitoring System

Note to the reader

1. This synthesis discusses a total of 10 publications. They are all open access with the respective links throughout each relevant section and bibliography. It is advisable these are read before or during their respective chapter.
2. Academic writing is traditionally written in the third person, such as a traditional PhD thesis. However, to fulfil a PhD by publication requirements, this Critical Overview document was created with the objective of outlining my work and contributions to the field as well as my career development as a researcher. Therefore, first person will also be used throughout this document in the “Reflection” sections.

Introduction

Background

Deterioration detection and action on physiological indicators of worsening illness in acute hospital wards is a challenge acknowledged for more than 25 years (Mcquillan et al. 1998, Watkinson et al. 2006). Standard vital sign monitoring, namely pulse rate (PR) or heart rate (HR), respiratory rate (RR), blood pressure (BP), oxygen saturations (SpO2) and temperature, remain common practice throughout hospital and clinical facilities (National Institute for Health Care Excellence 2007, National Institute for Health and Care Excellence (UK) 2020). These can be measured either intermittently, through manual observations (the common practice in the general wards) or continuously using one or more automatic monitors (Hravnak et al. 2008). These observations can then feed into an early warning score (EWS), a known system which calculates a weight to each vital sign when there is a deviation from its normal value. EWS are recommended for routine hospital use in the UK (NICE Clinical Guidelines 2007) as it can guide the clinical response and escalation of care (National Institute for Health Care Excellence 2007, National Institute for Health and Care Excellence (UK) 2020). For example, the National Early Warning Score (NEWS) (Royal College of Physicians 2012) and its modification (NEWS2) (Royal College of Physicians 2017), are approved scoring systems in the UK for the identification of patient deterioration in a range of clinical conditions and environments (Scott et al. 2020, Smith et al. 2013, Spångfors et al. 2016, Pimentel et al. 2019).

In the general ward environment, as common practice is manual intermittent vital sign measurements by the clinical staff, EWS are dependent on the correct and individualised monitoring frequency (Jansen and Cuthbertson 2010). A known limitation is that manual measurements (including application of devices and documentation of results) can be time consuming for healthcare professionals and, consequently, the optimal monitoring frequency is often missed (Cardona-Morrell et al. 2016). Of more concern is that even when ideal frequency is achieved, patients might deteriorate between intermittent observation sets (Tarassenko, Hann, and Young 2006).

Patients at higher risk are often continuously monitored, improving early detection of deterioration (Prgomet et al. 2016). However, in the UK, this type of monitoring is not commonly used in the ward environment (Bonnici et al. 2013). Downey et al. suggested in their review that continuous vital sign monitoring outside the intensive care has the potential to improve patient outcomes when compared with intermittent monitoring (Downey, C.L. et al. 2018b, Javanbakht et al. 2020). A later study also indicated that implementing continuous monitoring in surgical wards was cost effective (Javanbakht et al. 2020). However, interviews with nurses and other clinical staff suggested that despite the

potential to increase the timely detection of patient deterioration, limitations in automatic vital sign monitoring technology can pose a barrier to implementation (Prgomet et al. 2016). Current literature highlights some of the potential challenges, such as the invasiveness of traditional wired continuous monitors (Bonnici et al. 2013, Downey, C.L. et al. 2018b), as they can restrict patient mobility and independence in the general ward environment, thus affecting its compliance (Baig et al. 2017, Pavic et al. 2019). Another limitation is the high rate of false alerts, which can also be detrimental to both the patient and clinical staff (Görges, Markewitz, and Westenskow 2009, Bonafide et al. 2015, Drew et al. 2014, de Man et al. 2013).

In response to these limitations in healthcare monitoring, companies are extending the capabilities of commercially available wearable vital sign monitoring systems (Appelboom et al. 2014). Wearable devices might have the potential to bridge the gap between intermittent manual observations and traditional wired continuous monitors (Weenk et al. 2017). These can perhaps improve patient safety and earlier detection of deterioration through continuous monitoring, while optimising clinical staff time and promoting patient mobility and independence using wireless devices (Weenk et al. 2017). However, there is still limited evidence on the feasibility of its implementation in the hospital environment (Leenen et al. 2020), there is even less research on its clinical impact as most systems seem to be in the technology validation phase, with few studies focusing on clinical outcomes (Leenen et al. 2020, Sun et al. 2020). And while there are many wearable devices and companies claiming the ability to safely monitor patients at risk of deterioration (Naziyok, Zeleke, and Röhrig 2016), evidence assessing the impact of ambulatory monitoring systems in clinical outcomes remains inconclusive, limiting its implementation and clinical use (Naziyok, Zeleke, and Röhrig 2016).

The virtual High Dependency Unit (vHDU) project is a multidisciplinary collaborative effort between the Critical Care Research Group (CCRG) from the Nuffield Department of Clinical Neurosciences and the Institute of Biomedical Engineering (IBME), University of Oxford. This team includes doctors, nurses, and allied health professionals (AHPs) specialised in emergency and critical care, as well as engineers, statisticians, and methodologists. This project was created with the overall objective to develop and test the feasibility of a wearable monitoring system (WMS), the vHDU system, in the general ward environment and assess its clinical impact on early deterioration detection and associated clinical outcomes.

Portfolio and objectives

This portfolio includes a selection of my publications throughout the vHDU project (table 1). This synthesis will explore their relationship and build a coherent thread of the pipeline development and impact of my work. It contains seven chapters and a total of 9 peer-reviewed publications and 1 pre-print (currently in the 2nd peer review-round):

Chapter	#	Journal, year and impact	Title and link	Ref
1	P1	BMJ Open 2021 Impact factor: 2.692	Protocol for a systematic review assessing ambulatory vital sign monitoring impact on deterioration detection and related clinical outcomes in hospitalised patients.	(Areia, Carlos et al. 2021c)
	P2	BMC Critical Care 2021 Impact factor: 9.097	The impact of wearable continuous vital sign monitoring on deterioration detection and clinical outcomes in hospitalised patients: a systematic review and meta-analysis.	(Areia, Carlos et al. 2021a)
	P3	BMC Critical Care 2021 Impact factor: 9.097	Continuous wireless postoperative monitoring using wearable devices: further device innovation is needed.	(Xu et al. 2021)
2	P4	Journal of Advanced Nursing 2021 Impact factor: 3.187	Experiences of current vital signs monitoring practices and views of wearable monitoring: A qualitative study in patients and nurses.	(Areia, Carlos et al. 2021b)
3	P5	JMIR mHealth and uHealth 2020 Impact factor: 4.770	Wearability Testing of Ambulatory Vital Sign Monitoring Devices: Prospective Observational Cohort Study.	(Areia, Carlos et al. 2020b)
4	P6	BMJ Open 2020 Impact factor: 2.692	Protocol for a prospective, controlled, cross-sectional, diagnostic accuracy study to evaluate the specificity and sensitivity of ambulatory monitoring systems in the prompt detection of hypoxia and during movement.	(Areia, Carlos et al. 2020a)
	P7	JMIR 2021 Impact factor: 5.430	Chest patch for continuous vital-sign monitoring: A clinical validation study during movement and controlled hypoxia.	(Morgado Areia et al. 2021)
	P8	JMIR 2022 Impact factor: 5.430	Wearable pulse oximeters in the prompt detection of hypoxaemia and during movement: a diagnostic accuracy study.	(Santos, M. et al. 2021)
5	P9	Frontiers in Digital Health 2021 Impact factor: none yet	A Real-Time Wearable System for Monitoring Vital Signs of COVID-19 Patients in a Hospital Setting.	(Santos, M. D. et al. 2021)
6	P10	Submitted to Pilot and Feasibility studies journal (2022)	Pre-print (in review): Impact of an Ambulatory Monitoring System on Deterioration Detection and Clinical Outcomes in Hospitalised Patients. A Feasibility Randomised Controlled Trial Protocol.	(Areia, Carlos et al. 2022)
7	***Final reflection***			

Table 1 – List of publications.

This synthesis aims to present the pipeline work from the vHDU project, from device selection, testing, system development and integration, implementation, and future work. Objectives include:

1- To assess current evidence on the impact of WMS in deterioration detection and associated clinical outcomes versus standard care (**Chapter 1**).
2- To understand patient and clinical staff experiences of current practice and views of WMS (**Chapter 2**).
3- To test the wearability of selected wearable monitoring devices (**Chapter 3**).
4- To test the measurement accuracy of selected wearable monitoring devices (**Chapter 4**).
5- To integrate final wearable devices, develop vHDU system and outline implementation process during COVID-19 (**Chapter 5**).
6- To design a feasibility RCT testing the vHDU system against standard care (**Chapter 6**).
7- Outline each publication and overall project contributions to the field, as well as my own development as a clinical academic researcher throughout this project (**Chapter 7**).

This portfolio of publications should constitute an equivalent body of work of a traditional PhD.

Summary of chapters and contributions

Figure 1 provides a flowchart of the link between chapters/publications, with a more descriptive visual guide in Appendix 1. Besides the individual contribution of each chapter and respective studies, the pipeline of publications and the critical analysis included in this synthesis provide detailed information on the processes and lessons learned in the testing, development, and clinical implementation of a WMS in the hospital ward environment.

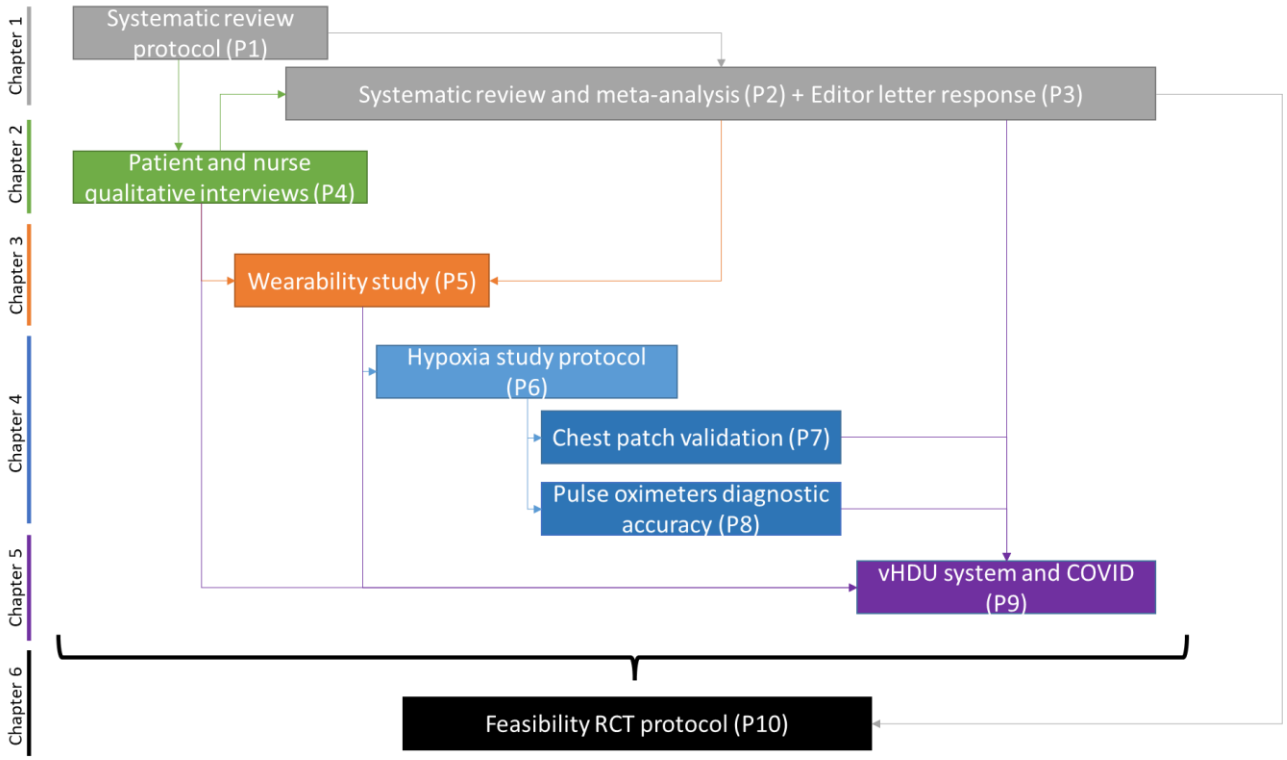


Figure 1 – Doctoral synthesis chapters and publications flow-diagram.

Chapter 1 highlights the lack of current evidence on the superiority of WMS over standard care, through a comprehensive systematic review and meta-analysis. ***P1*** is the review protocol providing a thorough methodological description of the process and aims for both the meta-analysis and narrative synthesis. ***P2*** is the systemic review and meta-analysis, highlighting the literature gap and the need for high quality trials to answer the research question. It also provides secondary information on included WMS studies, that we used throughout the vHDU project. ***P3*** includes a response to a letter to the editor, reinforcing the need to test and use WMS as a complement, and not a substitute, to standard care.

Chapter 2 builds on the gap identified in chapter 1, exploring both clinical staff and patients' experiences of using current monitoring practices and their early thoughts on WMS use in the ward environment. This chapter includes one publication (***P4***) that explores the clinical behaviour and challenges on current vital sign monitoring practices, supporting researchers in identifying gaps that can be filled with wearable technology and important aspects of WMS implementations (such as views on not replacing direct nursing contact, reinforcing chapter 1 conclusions).

These two chapters (1 and 2), and respective publications, focused on identifying and discussing gaps in the literature, both for current monitoring practices and WMS clinical implementation. They provided early data not only on the state of evidence in the field, but also practical local knowledge on what and how we should develop and test WMS. Considering this, **chapter 3** contains another

publication (***P5***), one of the few available studies in the literature testing devices wearability. Our results reinforce the importance on the balance between devices accuracy and comfort to maximise worn times and, consequently, data acquisition. The results suggested that pulse oximeters without a fingertip compressing probe were preferred, as well as a small patch. This study narrowed our list of potential vital sign monitoring devices from 7 to 5 devices, subjected to accuracy testing.

Chapter 4 harnesses the information from chapter 1 and tests the finally selected 5 devices from chapter 3. This chapter includes one of the most challenging and innovative accuracy studies within this project. The selected devices were submitted to movement and controlled moderate to severe hypoxia testing, in comparison to both clinical and gold standard devices for HR, RR and SpO2. Due to its complexity, the protocol outlining the rationale and methodological procedures for the "Hypoxia study" was early published (***P6***). Two analyses resulted from this: in ***P7*** the chest patch was validated in accordance with ANSI/AAMI EC13:2002 standards and in ***P8*** the accuracy of 3 out of the 4 tested pulse oximeters was confirmed according to the ISO 80601-2-61:2019 guidelines. These confirmed devices' performance during movement and hypoxia, supporting their clinical use in populations with high risk of desaturation.

Chapters 3 and 4 focused on the selection and testing of commercially available devices. The aim was to find a thoughtful balance between wearability and accuracy of these devices to select the most appropriate to incorporate the vHDU system. Using this information, **chapter 5** describes the process of the final device selection, integration, and development of the vHDU system(***P9***). It provides information on the prompt deployment in the COVID-19 wards, to support staff minimising their exposure while continuously monitoring patient HR, RR and SpO2 using the vHDU system. The contributions of ***P9*** work are numerous, including all the technical and practical information for WMS deployment. This was the culmination of the work described in chapters 1-4, which was crucial to the rapid and successful implementation of the wearable monitoring system we developed during this unprecedented emergency.

Chapter 6 aggregates the above work and describes in detail the design for a feasibility RCT (***P10***). This study will not only gather initial data testing the vHDU system vs standard care but also provide secondary data on other clinical and practical outcomes, such as its feasibility to move to a well powered multicentre RCT, that will contribute to the gap of evidence highlighted in **chapter 1.**

Chapter 7 includes a final critical analysis of all the work, links within these publications and its contribution to the field of wearable monitoring. It also explores both my own contributions as well as my growth and development as a clinical researcher throughout each study and the overall vHDU project.

Autobiographical context of the portfolio

Early career

Physiotherapist by background, my early career was mostly clinical between 2013 and 2016; having worked in several hospitals, clinics, and sports clubs in Portugal. In 2016 I moved to the UK where I continued my physiotherapy work. My first contact with research happened during my ERASMUS programme at Southampton University, in 2013, doing a qualitative systematic review (Demain et al. 2015) and then later, in my MSc thesis, where I conducted a cross-sectional study of young athletes with and without a particular musculoskeletal injury (Areia et al. 2019a). These early experiences inspired me to seek a clinical academic career.

To achieve this, in late 2016, I gained a role as a Clinical Trial Manager for a national multicentre RCT, recently published in The Lancet journal (Beard et al. 2022); this turned my research spark into a small flame, that gradually grew as the RCT developed through protocol design, ethical approvals and patient recruitment and study management activities. Although I enjoyed working in a big RCT, I decided to welcome a new opportunity by moving to more applied research in the wearable monitoring field and joined the Critical Care Research Group (CCRG) at Oxford University in late 2018, just when the vHDU project was about to start.

Portfolio work

By getting involved in several studies simultaneously from the beginning (inside and outside the vHDU project) I quickly realised that I needed a better understanding of data and statistical knowledge, that steered me into initiating a postgraduate certificate in Health Data Analytics at University College London (UCL) in 2019.

Responsibilities when I started in the vHDU project included supporting and coordinating current studies, such as the clinical staff qualitative interviews (**chapter 2**) and the wearability study **(chapter 3)**. That gave me a very good early insight into the main research question for this project, its vision and end goal. However, it was at this point that I identified a big gap in this project and current literature in the field, on the current impact of WMS in deterioration detection and associated clinical outcomes. I thought it would be sensible to also conduct a systematic review to understand the current state of evidence (**chapter 1**) and offered to lead it. Soon after, I also started contributing to the design of the Hypoxia study (**chapter 4**) and leading its day-to-day management during recruitment. I have searched for ways to develop and grow with the project through management, leadership, data analytics and statistics courses and ended up conducting the analysis for most of these studies (and establishing my interest in data analysis).

By early 2020, the small research flame was now fully bursting, and I was designing and leading multiple studies and analysis within the vHDU project. During this, I also started showcasing my work at national and international conferences. Then, the COVID pandemic arrived, and like most research activities around the world, we had to pause participant recruitment in the vHDU project, and all other studies ran by our group. This allowed us to focus our efforts on finalising the monitoring system and work with the clinical staff to quickly implement it in the COVID isolation wards (**chapter 5**). This was one of the most exciting and scary periods of my career both as a clinician and researcher (reflected throughout this synthesis). The pandemic implementation work and real-time impact inspired me to push forward the design of a feasibility RCT, explored in **chapter 6**, where all our work converges. Having previously designed systematic reviews, surveys, interventional and diagnostic studies, the design of an RCT marked another individual goal of my career.

I am an advocate for methodological quality in digital health implementation projects and data analytics knowledge amongst nurses and health professionals. I also maintain my tutoring and teaching activities and contribute to multiple digital health projects, through consultancy and academic work. Alongside my academic and data science career, I still keep some clinical work, as I believe maintaining patient contact greatly contributes to my research activities, as well as my research and academic knowledge also play a role in my clinical decision making (Cowley et al. 2020, Trusson, Rowley, and Barratt 2021, Chalmers 2022).

Chapter 1:

Current evidence of wearable monitoring systems impact on deterioration detection

Context and objective

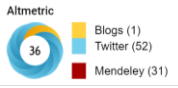
While designing the vHDU studies, it was important to understand the current state of knowledge of the impact of WMS in clinical deterioration detection and associated outcomes, as well as an overview of the wearable monitoring devices and systems being used by other teams around the world working in the field. Previous research indicated that WMS might have the potential to promote early deterioration and impact patient outcomes, such as decreased mortality, intensive care admission, rapid response team activation and hospital length of stay (Sun et al. 2020). However, most wearable devices seem to be in the development and technological validation stages, with few studies assessing its clinical impact, despite the exponential growth of commercially available devices, there seems to be a gap on WMS implementation in the hospital environment (Leenen et al. 2020, Sun et al. 2020, Naziyok, Zeleke, and Röhrig 2016).

To better explore this, a systematic review and meta-analysis was designed with the objective to assess the impact of vital sign monitoring on the detection of physiological deterioration and related clinical outcomes of hospitalised patients using WMS in comparison with standard care. The protocol was registered in PROSPERO (CRD42020188633), and the result published in a peer-reviewed journal (Areia, Carlos et al. 2021c).

P1: Published protocol

BMJ Open 2021 Impact factor: 2.692	Protocol for a systematic review assessing ambulatory vital sign monitoring impact on deterioration detection and related clinical outcomes in hospitalised patients **Areia C,** Vollam S, Young L, Biggs C, Pimentel M, Santos M, et al.	 **2 citations**

P2: Published systematic review and meta-analysis

BMC Critical Care 2021 Impact factor: 9.097	The impact of wearable continuous vital sign monitoring on deterioration detection and clinical outcomes in hospitalised patients: a systematic review and meta-analysis. **Areia C,** Biggs C, Santos M, Thurley N, Gerry S, Tarassenko L, Watkinson P, Vollam S.	 **7 citations**

P3: Published response to letter to editor

BMC Critical Care 2021 Impact factor: 9.097	Continuous wireless postoperative monitoring using wearable devices: further device innovation is needed. Xu W, Ghabirans A, Bissett I, O'Grady G, Wells C, **Areia C**, Biggs C, Santos M, Thurley N, Gerry S, Tarassenko L, Watkinson P, Vollam S.	 **2 citation**

Table 2 – Chapter 1 included publications with citation and mentions information. Extracted 05th November 2022.

Results

This meta-analysis analysed 8706 citations and included 10 studies. Our results highlighted the lack of evidence on WMS superiority over standard care for early deterioration detection and associated clinical outcomes (although there was some non-statistically significant trend towards its positive impact) (Areia, Carlos et al. 2021a). Due to the heterogeneity among the included studies design, quality and outcome measures, it was not possible to reach a definite conclusion on whether WMS implementation can positively impact patient safety and care, emphasising the need for more and better research to confirm this (Areia, Carlos et al. 2021a).

A "letter to the editor" was received from a research team in New Zealand, defending that we are not yet at the stage of conducting well powered RCTs and more validation studies are required to ascertain devices accuracy (Xu et al. 2021). Our published response clarified an important aspect of our (and other researchers, as highlighted in this review) work, also emerged in our qualitative study (explored in **chapter 2**). Currently, due to the lack of evidence supporting its superiority, WMS should not be tested and/or implemented in the hospital as a "stand-alone" method for vital sign measurement. It should instead be used as a support, and not a replacement, for standard care, due to current technology uncertainties and limitations (such as WMS accuracy and reliability).

Contribution to knowledge and originality

This systematic review highlighted important points that were crucial for the development of our wearable monitoring system (vHDU system) and will support further research in the field:

1. Agreed with previous research supporting that most WMS are still in the feasibility testing phase and few have been implemented or tested in a clinical environment (Areia, Carlos et al. 2021a, Leenen et al. 2020) and there is an urgent need for high quality studies comparing WMS vs standard care, to prove its impact in hospitalised patients' safety and support its implementation, encouraging our future work (**chapter 6**).
2. Aggregated important information on alerting systems, such as thresholds, iterations, alert rates, among others. This was not only crucial for the design of our vHDU system (**chapter 5**), but may also support future studies and innovations, by learning processes and lessons learnt from previous similar research included in this review, such as reducing the rate of alerts to avoid alarm fatigue from the clinical staff (Areia, Carlos et al. 2021a, 2021b).
3. Reiterated the importance to test and implement wearable technology as a complement, and not a substitute to standard care, due to concerns around devices accuracy (Xu et al. 2021) and direct contact disruption (see **chapter 2**).

4. Emphasised the importance of publication transparency by analysing clinical trial registration information and identifying studies that were registered but not published. For example, we found most included studies were not registered prospectively. We also identified four studies that might have contributed to this systematic review, highlighting this under-reported and non-published evidence, which could have potentially impacted our results.

Although this meta-analysis (***P2***) was recently published (September 2021), our paper has already been externally cited by several research teams (Yizhe 2021, Leenen et al. 2022a, 2022b, López-Espuela et al. 2022, Aagaard et al. 2022, Tange Larsen et al. 2022), supporting its recognition by the scientific community and its contribution to the field. Similarly, our response letter (***P3***, published in December 2021) has also been used by our New Zealand colleagues (Wells et al. 2022, Xu et al. 2022).

Reflection

The systematic review suggests there is currently no evidence to support the use of WMS for deterioration detection and associated outcomes over standard care. These results are not unexpected, and highlights the need for more and better studies, building a case for our feasibility RCT (explored in **chapter 6**). By aggregating WMS information and contacting the authors during this review, I collected several practical insights and lessons (e.g. appropriate team presence during WMS implementation, refining alerting systems, among others) from other research teams working in the field, that helped us build our WMS.

Additionally, this review adds something that I have never seen elsewhere, which is the inclusion of studies registration details and the ratio of registered/published studies. This was an important step in ensuring rigour and assessing publication bias (Viergever and Ghersi 2011). Hopefully, other reviews will follow this example and conduct a trial registry review as part of their work, encouraging researchers to publish and share what they registered. This also made me reflect on the challenges of conducting clinical trials in the field, as none of the included studies addressed any potential operational and practical confounders that can be present in the hospital environment, such as staff capacity, time of event (day vs night shift), staff seniority throughout patient stay, local ICU and ward capacities, the Do Not Attempt Resuscitation (DNAR) status of patients who died, among many others that could significantly impact and bias results. Although we made efforts to minimise this during the design of our RCT (**chapter 6**), one must acknowledge it is practically impossible to address all potential confounders and trials need to be pragmatic in nature.

In summary, this review nicely complemented our vHDU project by highlighting the lack of statistical evidence in the field and providing important data to the development and implementation of our WMS, setting the field for next chapters' work.

Chapter 2:

Clinical staff and patient views of current monitoring practices inside the hospital, and early views on WMS

Context and objective

For successful implementation of a new WMS, it is important to understand current vital sign monitoring practices and how to best plan this new technology implementation in the ward environment, avoiding disruption of current practices and protocols as well as resistance from the clinicians and patients using it (Taenzer et al. 2011, Lewy 2015). To fill this knowledge gap and to better understand our local practices and procedures, this qualitative study interviewed 15 nurses and 15 patients in a local surgical ward with the objective to understand their experiences of current monitoring practices. We have also taken this opportunity to explore early views on the introduction of wearable monitoring in their ward.

P4: Qualitative study

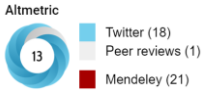
Journal of Advanced Nursing 2021 Impact factor: 3.187	Experiences of current vital signs monitoring practices and views of wearable monitoring: A qualitative study in patients and nurses. **Areia C,** King E, Ede J, Young L, Tarassenko L, Watkinson P, Vollam S.	 **8 citations**

Table 3 - Chapter 2 included publication with citation and mentions information. Extracted 05th November 2022.

Results

The results provided the qualitative groundwork that informed our vHDU project throughout, as the following interconnected themes were identified:

- Vital sign data as evidence for escalation
- Trustworthiness of vital sign data
- Finding a balance between continuous and intermittent monitoring

Introduction of the concept of ambulatory wearable devices and WMS was viewed positively by both groups as offering solutions to some of the issues identified with traditional wired monitoring through the interviews. However, most agreed that this would not be suitable for all patients and should not replace direct nurse/patient contact. Previous studies support that WMS have the potential to facilitate earlier deterioration detection and improve patient safety without posing a barrier to mobility, as well as reduce staff workload and hospital costs (Weenk et al. 2020, Joshi et al. 2021, Olsson et al. 2018, Downey, C.L. et al. 2018a), reinforcing the direction of our findings in this study (further explored in **chapter 7**).

Contribution to knowledge and originality

Besides providing a solid qualitative foundation of current nurses and patient experiences for our vHDU project, this work highlighted several points that are crucial for both clinicians and researchers in the field:

1- Nurses frequently use vital sign data to support their concerns and facilitate escalation.
2- When in doubt, nurses seem to revert to manual monitoring.
3- Wearable technology was seen positively by both nurses and patients to bridge the gap between traditional wired continuous systems and manual observations.
4- Wearable technology should complement, and not replace direct contact between nurses and patients.
5- Wearable technology should not add more noise to the already loud ward environment.

This analysis raised helpful insights for our vHDU system, for example one of the challenges most frequently reported by the nursing staff was not being able to escalate a patient to a senior clinician when the patient was not triggering (triggering is the clinical slang for a patient with EWS above the normal threshold). Since this concern is not new (Ede et al. 2020), the "nurse-worry" factor (Romero-Brufau et al. 2019) should be considered and integrated into WMS. Another interesting finding from the interviews was the trustworthiness of vital sign data from the nursing staff, often reverting to manual measurements as soon as they suspect something is wrong (eg. faulty device, or vital sign is not consistent with patient condition). This was considered during the vHDU system development, that incorporated both continuous and manual vital sign data (**chapter 5**). Finally, as discussed above, other alerting stimuli was suggested to avoid further noise in the already loud ward environment, and therefore vibration and visual cues were explored during system development.

Despite this study being only published in October 2021, it has already been externally cited by 6 publications (Vuillaume et al. 2022, Wells et al. 2022, Leenen et al. 2022a, Iqbal et al. 2022, Heydari Beni and Jiang 2022, Ullah et al. 2022), including a recent study on nurses' perceptions of behavioural factors that influence continuous wearable vital sign monitoring systems on general surgical wards (Leenen et al. 2022a). Similar themes to our study were identified and discussed by Leenen et al., for example, the interpretation of vital sign trends, its challenges and using it to support nurse worry and patient escalation, reducing false alarms and noise in the ward, WMS not being suitable for all patients nor being a substitute to direct care and clinical judgement (Leenen et al. 2022a).

Reflection

This study provides the qualitative groundwork underpinning the vHDU project and presented insights that myself and the team used throughout vHDU system development and integration. Our findings also highlighted the importance of mixed-methods research when testing and integrating new technology in a clinical environment and encouraged the continuing interviews and focus groups throughout our project, promoting a close collaboration with both patients and clinical staff.

In particular, the theme *Trustworthiness of vital sign data* triggered my interest, when nurses shared their perceived accuracy of vital sign measurement methods, with most agreeing to commonly double check or revert to manual readings for most vital signs when they suspect the device is unreliable or they feel something is not right (Cardona-Morrell et al. 2016, Areia, Carlos et al. 2021b). They also felt some traditional methods of vital sign monitoring to be unreliable, and commonly disregard its measurements (such as continuous RR through a 3-lead ECG). The present qualitative study discusses that although there is a variety of evidence testing the accuracy and validating different methods for each vital sign monitoring, very little is known about the perceived trustworthiness by clinical staff, despite these methods being part of their daily practice (Areia, Carlos et al. 2021b). Considering this, I designed a service evaluation study to survey the perceived trustworthiness of each vital sign monitoring method in our local Trust. The survey is now finished, with over 700 clinical staff members completing it, and results will be submitted to peer-review soon.

In summary, this study provided the foundational practical evidence needed for our vHDU project, with qualitative data on local current monitoring practices, protocols and current challenges felt by both staff and patients. This allowed us to better understand how to support practice, what was important for the potential users of the vHDU system, and what should be tested and developed in the next studies.

Chapter 3:

Initial device selection and wearability testing

Context and objective

The previous chapter results indicate that one can have the most medically accurate device available, however, if it is not comfortable, patients will keep removing it, or not wear it at all (Jeffs et al. 2016). A previous study has also shown evidence that devices are removed prematurely owing to patient irritation, discomfort, feeling unwell, or equipment failure (Jeffs et al. 2016). Additionally, it has been suggested that introducing unknown devices into the ward environment may have physical or psychological effects that should be assessed to maximize patient compliance and data acquisition (Cancela et al. 2014, Knight and Baber 2005, Knight et al. 2002).

A thoughtful balance is needed between wearability and accuracy of devices for successful system integration and deployment (Areia, Carlos et al. 2020b). For this reason, another study of the vHDU project was to test the wearability of selected commercially available devices. The selected devices included two chest-worn patches: VitalPatch (VitalConnect) and Peerbridge Cor (Peerbridge) collecting HR and RR, and 5 pulse oximeters, with 4 wrist-worn devices with finger probe: Nonin WristOx2 3150 (Nonin), Checkme O2+ (Viatom Technology), PC-68B, and AP-20 (both from Creative Medical); and 1 solely wrist-worn device: Wavelet (Wavelet Health), all collecting PR and SpO2.

P5: Wearability study

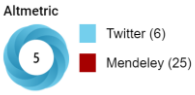
JMIR mHealth and uHealth 2020 Impact factor: 4.770	Wearability Testing of Ambulatory Vital Sign Monitoring Devices: Prospective Observational Cohort Study. **Areia C**, Young L, Vollam S, Ede J, Santos M, Tarassenko L, Watkinson P.	 **12 citations**

Table 4 - Chapter 3 included publications with citation and mentions information. Extracted 05th November 2022.

Figure 2 – Devices subjected to wearability testing. Extracted from P5 (CC-BY 4.0) (Areia, Carlos et al. 2020b)

Results

Twenty healthy volunteers wore each device for up to 72 hours while performing usual "activities of daily living" and were asked to complete a short survey per device regarding their comfort and general wearability. A total of 70 questionnaires (approximately 10 per device) were completed in this study. From the pulse oximeters, the Wavelet (wrist only) was the clear favourite as it did not have a finger probe compressing the finger. Amongst pulse oximeters with a finger probe, the CheckMe O2+ was suggested to be the most wearable, probably due to the smaller and ring-shaped finger probe, with placement away from the fingertip (Figure 3).

Figure 3 - Comfort Rating Scale scores for each pulse oximeter. Green represents the percentage of positive outcomes and red represents the percentage of negative outcomes. Extracted from P5 (CC-BY 4.0) (Areia, Carlos et al. 2020b)

On the chest patches, there was indication of a preference towards the VitalPatch (Figure 4) (Areia, Carlos et al. 2020b). This study supported the initial selection of wearables to be submitted to accuracy testing (**chapter 4**) before integration into the vHDU system (**chapter 5**).

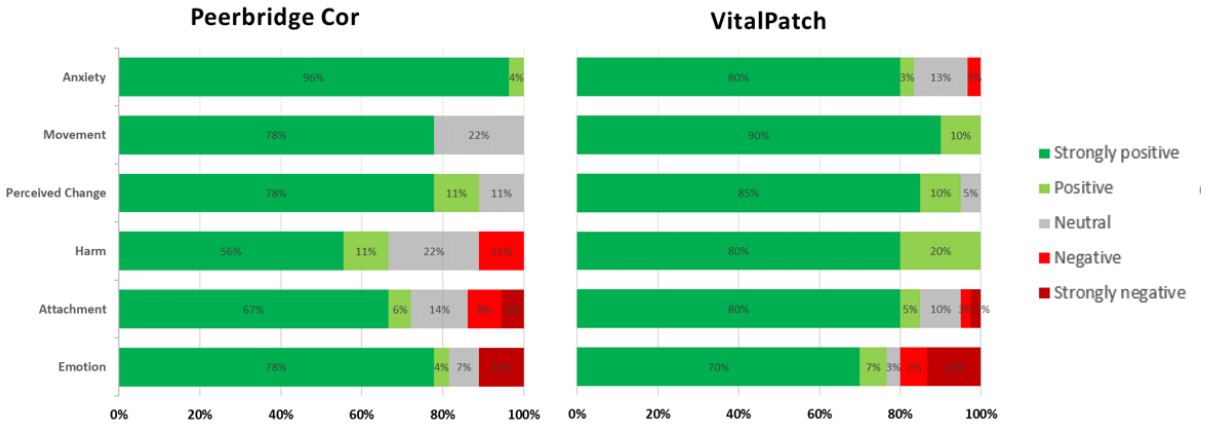


Figure 4 - Comfort Rating Scale scores for each chest patch device. Green represents the percentage of positive outcomes and red represents the percentage of negative outcome. Extracted from P5 (CC-BY 4.0) (Areia, Carlos et al. 2020b)

Contribution to knowledge and originality

It is known that wearability has a direct impact on system usability and its clinical implementation, as patients will be more likely to wear the device if they feel comfortable, thus improving data availability and quality (Baig et al. 2017). In addition to providing wearability data to select devices for accuracy

testing as part of this project, this study brought important contributions to the wearable technology field:

1- Highlighted the need for more wearability studies as part of devices evaluation, as to our knowledge, of the 7 included devices, only the VitalPatch had indexed wearability studies (Tonino et al. 2019, Selvaraj 2014).
2- Identified a clear preference towards pulse oximeters without a finger probe compressing the fingertip and a smaller, single use chest patch, providing potentially useful information for future wearables design.
3- Supported the need for a balance between wearability and accuracy before its implementation into the clinical environment; future researchers and companies should consider this during their design/testing.
4- Laid the groundwork for future wearability studies not only within the vHDU project (surgical patients), but also for other research teams working in different clinical scenarios.

Published in late 2020, this study is one of the most cited within the vHDU project, with 7 external citations from 6 publications (Wallace et al. 2021, Ede et al. 2021, Rosic et al. 2022, Rajbhandary et al. 2022, Hawthorne et al. 2022, Lee, Lee, and Park 2022) and one doctoral thesis (Holder 2022).

Reflection

Although there is an extensive growth of wearable devices, wearability studies remain scarce (Areia, Carlos et al. 2020b). For the initial selection of devices to be tested in this study we applied 3 main criteria for inclusion:

1. CE marked for medical use
2. Company provided raw data access
3. No data sent to third parties (collected data was kept locally inside the hospital servers)

One of the future considerations taken from this study is the use of the Comfort Rating Scale (CRS) (Knight et al. 2007, Knight and Baber 2005) for the main evaluation of devices wearability. As mentioned in the manuscript limitations, I believe the domains covered by this scale might not be the most appropriate for clinical monitoring devices wearability assessment, as applicability to the clinical environment might be limited (Areia, Carlos et al. 2020b). As a suggestion for future research, there is a need for the development of a new scale specific for wearable medical devices and monitoring systems, as I think it is a much-needed tool that will support testing and implementation of WMS. Another useful metric for our final device decision taken from this study were the “worn times” of

each device by participants, that together with the CRS scores, provided important information on which devices were more likely to be accepted by patients (**chapter 5**).

In summary, despite the lack of wearability studies in the literature, this study provided important wearability data on the selected devices, and, for our team, wearability testing was the logical next step in the vHDU project, as it supported the selection of devices to be put under accuracy testing, explored in the next chapter.

Chapter 4:

Devices accuracy testing

Context and objective

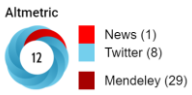
A known barrier to the clinical implementation of WMS is the uncertainty around devices reliability, efficiency, and data fidelity (Appelboom et al. 2014). Another challenge is the potential detrimental effect of movement on the data derived from such monitoring systems, for example, motion is known to affect the accuracy of pulse oximetry readings (Louie et al. 2018). This was seen throughout a clinically relevant range of measurements, with also less accuracy at lower arterial oxygen saturations (SaO2), which is clearly highly undesirable in clinical practice (Louie et al. 2018).

Considering this, the Hypoxia study was designed with the aim of testing the accuracy of selected devices from the wearability study (**chapter 3**). This includes 4 pulse oximeters, 3 with a finger probe (Nonin, AP-20 and CheckMe) and one without (Wavelet), and 1 chest patch (VitalPatch) versus clinical and gold standards (Table 5). This study involved the assessment of the diagnostic accuracy of the pulse oximeters and the validation of the chest patch; both during movement and under moderate (89% to 85% SpO2) to severe (<85% SpO2) hypoxia.

Vital sign	**Wearable devices**	**Clinical standard**	**Gold standard**
PR	AP-20 CheckMe Nonin Wavelet	Standard care pulse oximeter (Philips MX 450)	Arterial line trace
HR	VitalPatch	Standard care 3-lead ECG (Philips MX 450)	Standard care 3-lead ECG (Philips MX 450)
RR	VitalPatch	Manual respiratory rate per minute counting	Capnography
SpO2	AP-20 CheckMe Nonin Wavelet	Standard care pulse oximeter (Philips MX 450)	Arterial blood gas (SaO2)

Table 5 – Hypoxia study devices under test, clinical and gold standard for each evaluated vital sign.

P6: Hypoxia study protocol

BMJ Open 2020 Impact factor: 2.692	Protocol for a prospective, controlled, cross-sectional, diagnostic accuracy study to evaluate the specificity and sensitivity of ambulatory monitoring systems in the prompt detection of hypoxia and during movement. **Areia C**, Vollam S, Piper P, King E, Ede J, Young L, Santos M et al.	 **10 citations**

P7: Chest patch validation analysis

JMIR 2021 Impact factor: 5.430	Chest patch for continuous vital-sign monitoring: A clinical validation study during movement and controlled hypoxia. **Areia C**, Vollam S, Piper P, King E, Ede J, Young L, Santos M et al.	 **5 citations**

P8: Pulse oximeters diagnostic accuracy analysis

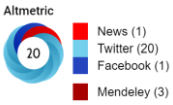
JMIR 2022 Impact factor: 5.430	Wearable pulse oximeters in the prompt detection of hypoxaemia and during movement: a diagnostic accuracy study. Santos M, Vollam S, Pimentel MA, **Areia C**, Young L, Roman C, Ede J, Piper P, King E, Harford M, Shah A, Gustafson O, Tarassenko L, Watkinson P.	 **4 citations**

Table 6 – Chapter 4 included publications with citation and mentions information. Extracted 05th November 2022.

Results

This study was conducted in 42 healthy volunteers and involved a single study visit where they used all the devices under test + clinical + gold standards while submitted to two testing stages (movement testing and hypoxia testing). Two analyses resulted:

- **Chest patch (VitalPatch) validation analysis**, where it was confirmed this chest patch reliably measured HR throughout all movements and hypoxia exposure and was also in agreement for RR throughout most movements (apart from the "sit to stand" and "turning a page") and hypoxia exposure (Figures 5 and 6), as per ANSI/AAMI EC13:2002 standards (Association for the Advancement of Medical Instrumentation 2002). This study also confirmed there was no impact on both HR and RR estimation performance when exposed to moderate and severe hypoxia, supporting its clinical use in patients with reduced baseline saturation or at risk of hypoxia (such as COVID-19 patients, discussed in **chapter 5**).

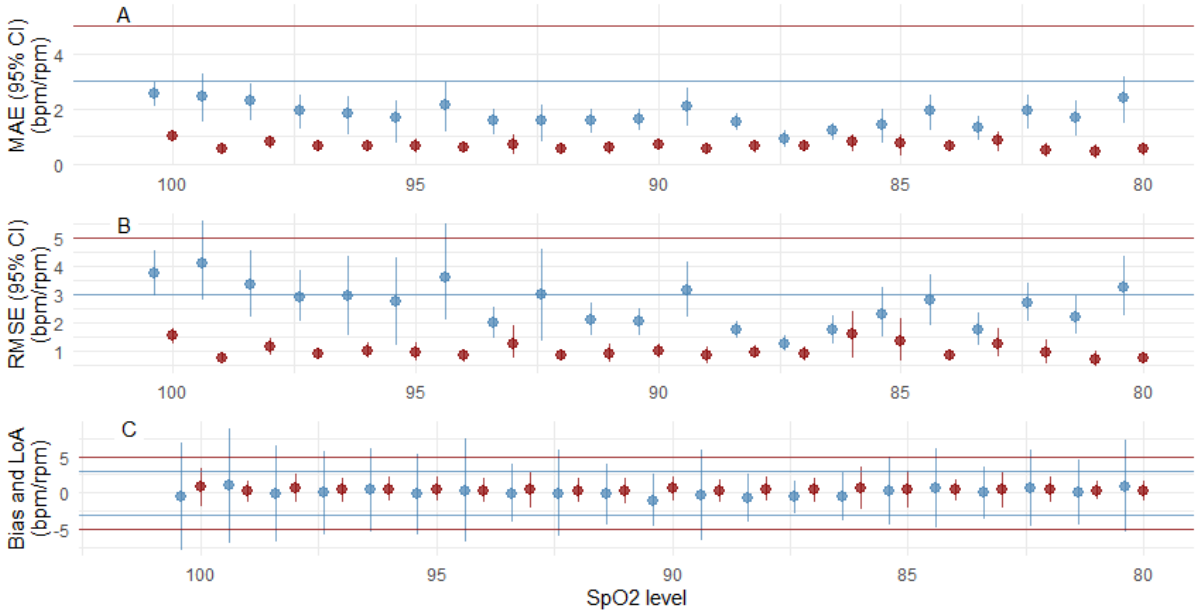


Figure 5 – VitalPatch Accuracy and Bias (mean bias) plots for the hypoxia phase. Red: heart rate; horizontal red lines represent acceptable limits (5 bpm) Blue: respiratory rate; horizontal blue line represents acceptable limits (3 rpm). (A) MAE (95% CI) plot, (B) RMSE (95% CI) plot, (C) bias LOAs. Bpm: beats per minute; LoA:s limits of agreement; MAE: mean absolute error; RMSE: root mean square error; rpm: respirations per minute; SpO2: peripheral oxygen saturation. Extracted from P7 (CC-BY 4.0) (Morgado Areia et al. 2021)

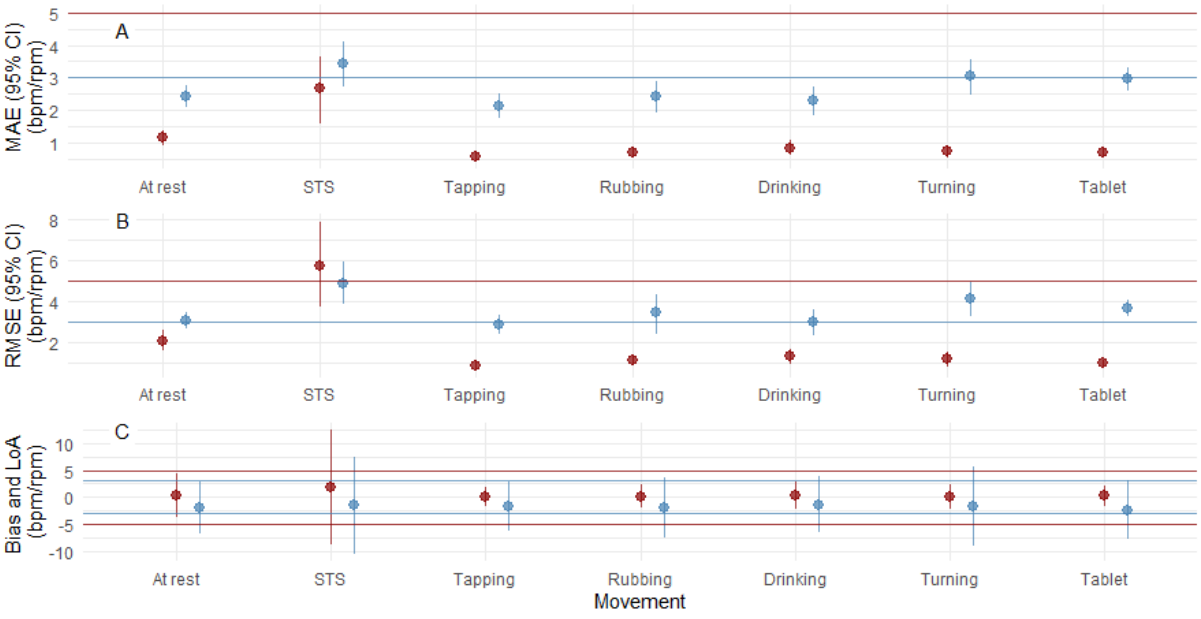


Figure 6 – VitalPatch Accuracy and Bias (mean bias) plots for all movement tests. Red: heart rate; horizontal red line represents acceptable limits (5 bpm). Blue: respiratory rate; horizontal blue line represents acceptable limits (3 rpm). (A) MAE (95% CI) plot, (B) RMSE (95% CI) plot, (C) bias LOAs. Bpm: beats per minute; LoAs: limits of agreement; MAE: mean absolute error; RMSE: root mean square error; rpm: respirations per minute; STS: sit-to-stand. Extracted from P7 (CC-BY 4.0) (Morgado Areia et al. 2021)

- **Pulse oximeters diagnostic accuracy analysis**, where it was concluded that all finger-worn pulse oximeters accuracy were within the required ISO guidelines (root-mean-square error, RMSE, below or equal to 4%, and below or equal to 8% when considering the confidence

interval, CI) when compared to clinical and gold standards, and all were able to detect hypoxaemia (Figure 7), despite performance was degraded by motion (Figure 8), but not significantly more than the clinical standard. To note is that the only pulse oximeter without a finger probe (Wavelet) included in this study did not achieve an acceptable level of accuracy and was therefore no longer considered for the vHDU system.

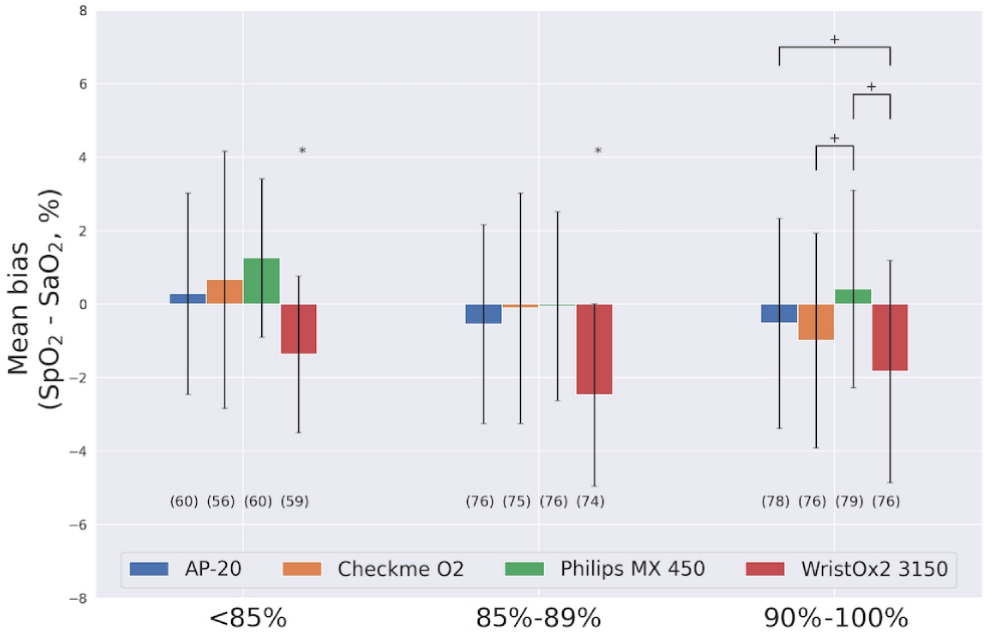


*Figure 7 – Pulse oximeters comparison of the mean bias (SpO2–SaO2) and precision for each of the four devices when compared to the gold standard for the 3 SaO2 subgroups: severe hypoxia, SaO2<85%; mild hypoxia, SaO2=85%-89%; and normoxia, SaO2=90%-100%. The number of points available per device is presented below each bar. For each subgroup, one-way ANOVA followed by the Tukey test was used to evaluate differences in the mean bias between devices. *Different from other values. +Different from each other. SaO2: arterial blood oxygen saturation; SpO2: peripheral oxygen saturation. Extracted from P8 (CC-BY 4.0)* (Santos, M. et al. 2021).

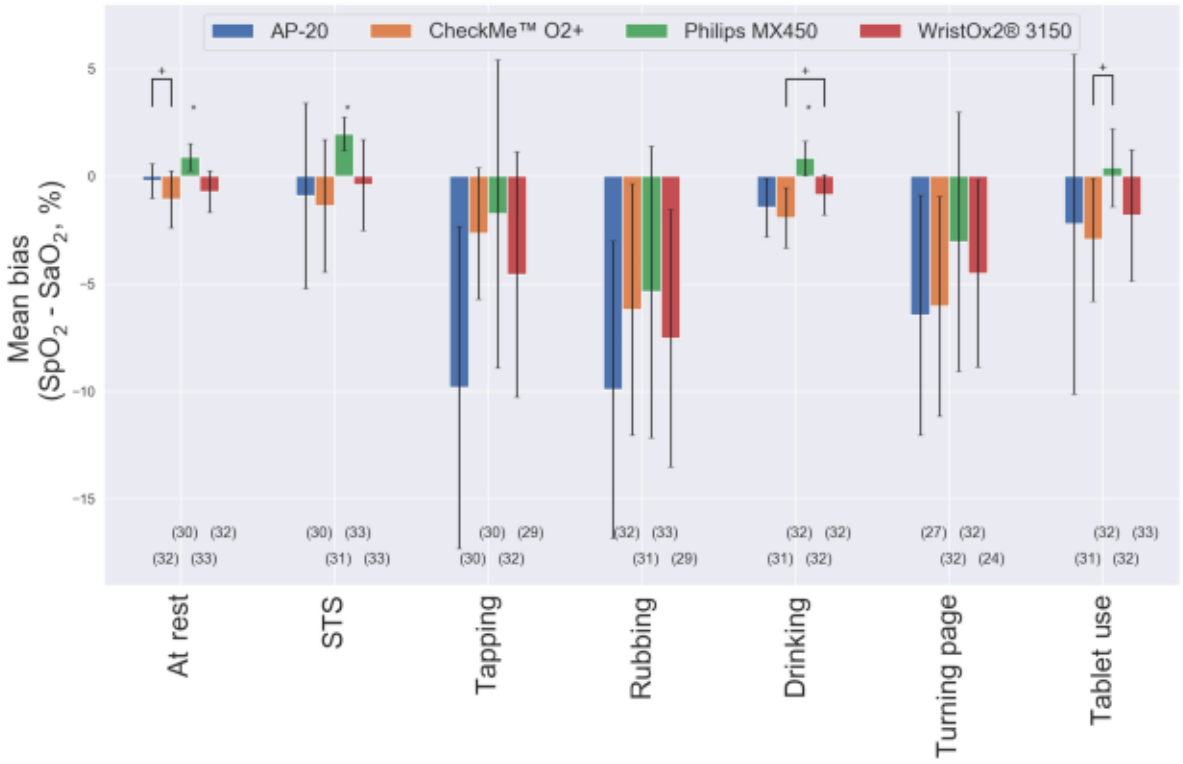


*Figure 8 – Pulse oximeters comparison of the mean bias (SpO2–SaO2) and precision for each of the four devices when compared to the gold standard for each movement type. The number of points available per device is presented below each bar. For each task, one-way ANOVA followed by the Tukey test was used to evaluate differences in the mean bias between devices. *Different from other values. +Different from each other. SaO2: arterial blood oxygen saturation; SpO2: peripheral oxygen saturation; STS: sit-to-stand. Extracted from P8 (CC-BY 4.0)* (Santos, M. et al. 2021).

Contribution to knowledge and originality

Following concerns around the accuracy of wearable devices for patient monitoring highlighted in **chapter 1**, the hypoxia study was an important piece of work not only for the vHDU project but also for the overall wearable healthcare monitoring field. Key contributions to knowledge include:

1- The protocol for this study promoted methodological transparency by thoroughly outlining study procedures and practicalities, facilitating its replication by other research teams.

2- Provided robust evidence and continuous monitoring data for 4 pulse oximeters and 1 chest patch during different standardised movements mimicking hospitalised patients, highlighting each device shortcoming during each movement when compared to the respective clinical/gold standard. This is an important aspect of WMS, to continuously monitoring patients, while simultaneously facilitating their mobility and safety (Joshi et al. 2019, Weenk et al. 2017, Verrillo et al. 2019).

3- Validated the VitalPatch against clinical and gold standard and supported its performance under movement and moderate to severe hypoxia, encouraging its use during the pandemic as part of vHDU deployment (**chapter 5**).

4- Thoroughly tested and confirmed the remaining pulse oximeters diagnostic accuracy and provided important vital sign and technical data on these devices, supporting its integration and use in **chapter 5**.

To our knowledge, it is one of the few studies providing accuracy data under controlled moderate and severe hypoxia, supporting the use of some devices in patients with high risk of acute desaturations. The need for these accuracy studies has become acute as health care systems have recommended the incorporation of ambulatory pulse oximeters in the home management of COVID-19 (Seshadri et al. 2020, Greenhalgh et al. 2020, O'Carroll et al. 2020). It was also a timely study for the vHDU project (discussed in the next chapter).

The protocol (***P6***) was published in January 2020, with 2 external citations (Tsai et al. 2021, Manta et al. 2020), one being an important study evaluating biometric technologies for vital signs during COVID, published in the peak of the pandemic (Manta et al. 2020). The chest patch analysis (***P7***) was published in August 2021, with 2 external citation (Lippi et al. 2022, Antikainen et al. 2022) and the pulse oximeter results (***P8***) in February 2022, with 2 external references (Rafl et al. 2022, Li et al. 2022). These external references used either technical data or study design methodologies from this study, supporting its early impact in the field.

Reflection

Considering all the above, this study was a central piece of the vHDU project. It is important to highlight that it was designed and conducted before the pandemic, and we were not aware of how important its results were going to be to the vHDU system development and prompt implementation in the COVID isolation wards (more in **chapter 5**).

One of the biggest challenges of this study was the organisational and operational skills required to ensure everything was conducted appropriately. This study involved a single study visit per participant and several variables needed to be considered for the efficient use of resources and staff. We required to rent a specific room in our local Cardiovascular Clinical Research Facility (CCRF) inside our local hospital to ensure all safety procedures were in place for the study visits. For each visit day at least 6 members of staff needed to be present, with a set of responsibilities each (full description can be found in the published protocol (Areia, Carlos et al. 2020a)):

- Senior anaesthetist: Medical cover.
- Engineer: Data and device monitoring.
- Researcher 1: Devices and timestamps.
- Researcher 2: Arterial Blood Gas (ABG) processing.

- Researcher 3: Participant activities and instructions.
- Researcher 4: Support/backup.

Another challenge was to ensure setup and kit were ready, including 4 pulse oximeters, 1 chest patch, clinical and gold standard monitors, 5 tablets, oxygen in nitrogen cylinder, hypoxicator, drip stand with arterial line, crash trolley and clinical kit (Figure 9). All devices, tablets and laptops were connected to the same network and time and date were set to Greenwich Mean Time Zone (GMT) or British Summer Time (BST) with a tolerance of ±2 seconds (Researcher 1 responsibility). All these methodological and operational challenges greatly contributed to the development of my project management and leadership skills (explored in **chapter 7**).

Figure 9 – Hypoxia study day set-up. Legend: 1: tablets linked with AMD devices (4 Samsung TAB A, each linked with one AMD: AP-20, WristOX2 3150 BLE, CheckMe™ O2 and VitalPatch®. 1 iPad four connected to the wavelet). 2: resuscitation trolley and oxygen. 3%–7% oxygen in nitrogen cylinder. 4: hypoxicator apparatus. 5: Philips monitor (model MX450) connected to laptop (IX trend software). 6: drip stand with the arterial line pressure bag. Extracted from the original protocol (CC BY 4.0) (Areia, Carlos et al. 2020a).

In summary, this study confirmed the SpO2 accuracy of 3 out of the 4 tested pulse oximeters according to the ISO 80601-2-61:2019 guidelines (Santos, M. et al. 2021) and the validation of the included chest patch (for HR and RR) according to the ANSI/AAMI EC13:2002 standards (Association for the Advancement of Medical Instrumentation 2002). Besides the overall contribution to the field, this study was crucial not only for the successful implementation of our system during COVID, but also to reassure clinical staff that these devices were clinically accurate and safe to use, discussed in the next chapter.

Chapter 5:

Final system and implementation during COVID-19

Context and objective

The Coronavirus disease 2019 (COVID-19) was declared a global health emergency by the World Health Organisation (World Health Organization 2020) at the beginning of March 2020. In the beginning, this pandemic presented several challenges for in-hospital patient care in the UK, the fear, both by patients and hospital staff, of the exposure and infection in clinical environments and the lack of knowledge about the severity and transmissibility of the virus and initial shortages of Personal Protective Equipment (PPE) are some examples (Ghanchi 2021, Willan et al. 2020).

Severely ill affected patients were filling ICUs, and those under observation were placed in isolation wards (National Center for Immunization and Respiratory Diseases - Division of Viral Diseases 2020). Our local hospital management were aware of the vHDU work on wearable monitoring, and by the end of February 2020, our team was tasked to supply isolation wards with a vital sign monitoring system. Six main requirements were established (Santos, M. D. et al. 2021):

1- As COVID mainly affects the cardio-respiratory system, target vital signs for continuous monitoring were SpO2, HR and RR.
2- Patients not confined to bed should be ambulatory.
3- Patient were to be remotely monitored in the closest nurse bay of the respective isolation rooms.
4- Any additional continuous monitoring from wearables should be fully integrated with the periodic nurse observations of the full set of vital signs, comprising SpO2, RR, HR as well as Blood Pressure (BP), Temperature (Temp), level of consciousness and the corresponding Early Warning Score (EWS) (Royal College of Physicians 2017).
5- The amount of contact between the infected patients and the nursing staff was to be minimised.
6- The system should work within the hospital cybersecurity infrastructure, compliant with patient confidentiality standards.

By the beginning of the pandemic the vHDU system was already capable of continuously monitoring SpO2, HR and RR, bringing the potential to facilitate mobilisation during continuous monitoring, considering device performance during movement (**chapter 4**) and providing real-time vital sign data at the bedside or remotely through a bespoke dashboard available in an open browser in the nurse's bay. Manual vital signs and other clinical measurements by the nurses was integrated into the vHDU

system as well (as per point 4). Our WMS was already integrated into the hospital IT systems and fully compliant with clinical governance and confidentiality requirements.

It was therefore clear that the vHDU system we had been developing to monitor high-risk patients in the surgical wards could be adapted to isolation patients monitoring in the COVID-19 pandemic, supporting both patient and clinical staff safety by minimising the amount of direct contact (Santos, M. D. et al. 2021). The objective of this manuscript was to provide an overview of our vHDU system, support device selection from our previous research (**chapters 1-4**), describe system optimisation to ensure it met the 6 aforementioned requirements, and describe the WMS deployment in the COVID-19 wards, with some preliminary data from the first wave of the pandemic.

Device selection

As the result of our wearability (**chapter 3**) and accuracy studies (**chapter 4**) the Vital Patch was the selected chest patch for HR and RR monitoring.

Of the 5 initial pulse oximeters, the PC-68B failed the wearability test (**chapter 3**), and the Wavelet was not sufficiently accurate in the detection of hypoxaemia (**chapter 4**). Leaving us with 3 options as a pulse oximeter, a) the AP-20, b) CheckMe O2+ and c) Nonin. From our wearability testing the Checkme O2+ was the clear favourite, due to the ring probe comfortability, as it was placed around the thumb and would not compress the fingertip like the other two remaining pulse oximeters (Areia, Carlos et al. 2020b). For the accuracy testing (**chapter 4**) these 3 devices showed statistically similar results during movement and hypoxia testing (Santos, M. et al. 2021).

From our results in **chapter 3**, the Checkme O2+ would provide more comfort while achieving a similar level of accuracy to other finger probe devices. However, there were a couple of practicalities on both the AP-20 and Checkme O2+ that would make them inferior to the Nonin device. In the early period of the pandemic, while the vHDU system was being developed to be implemented in the isolation wards, several focus groups (unpublished data) were held with the clinical staff of these wards. In some of them our engineers presented the 3 pulse oximeter finalists and their characteristics. Most staff agreed that having to charge, swap and reconnect devices was not feasible as battery life for Checkme O2 and AP-20 were less than a day of continuous use, which was counter-productive towards the deployment goals (reduce clinical staff exposure to the virus and maximise continuous patient monitoring time). On the other hand, the Nonin pulse oximeter only required 2 x AAA batteries to be swapped approximately every 48h of continuous use. In addition, it was also the only pulse oximeter that allowed consistent BLE communication and activated automatically once the patient's finger was

positioned within the probe. The Nonin was therefore the selected pulse oximeter (Figure 10) to be integrated in the vHDU system.

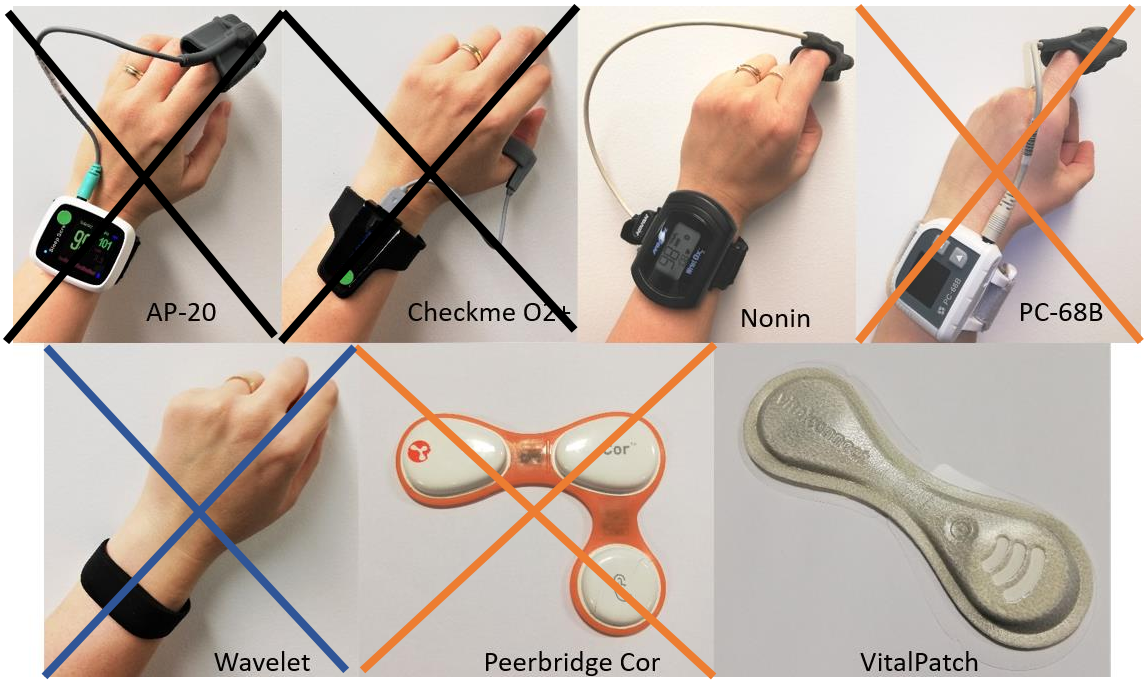


Figure 10 – Selection process of the final devices used in the vHDU system for the COVID implementation. Orange: excluded due to wearability results (P5), Blue: excluded due to accuracy (P8), Black: excluded after focus groups with clinical staff.

<u>P9 – vHDU system deployment during the pandemic.</u>

Frontiers in Digital Health 2021 Impact factor: none yet	A Real-Time Wearable System for Monitoring Vital Signs of COVID-19 Patients in a Hospital Setting. Santos M, Roman C, Pimentel M, Vollam S, **Areia C**, Young L, Watkinson P, Tarassenko L.	Altmetric 11 Twitter (15) Mendeley (32) **12 citations**

Table 7 - Chapter 5 included publication with citation and mentions information. Extracted 05th November 2022.

Results

Final system

As aforementioned, the Nonin (WristOx 3150 OEM BLE, Nonin Medical Inc., USA) (Nonin Medical Inc Plymouth U 2020) finger-based pulse oximeter, and the VitalPatch (VitalConnect, USA) (VitalConnect. n.d.) adhesive chest-patch were ultimately selected as our wearable devices. From the Nonin, the PR, SpO2 and near infrared PPG waveform were collected. From the VitalPatch we collected HR and RR, patient posture (e.g., standing, sitting, lying down, etc.), number of steps and the single lead ECG and 3-axis accelerometer waveforms. It also started to collect temperature in early 2021. These devices were connected to one tablet via Bluetooth, left inside the patient room (Figure 11).

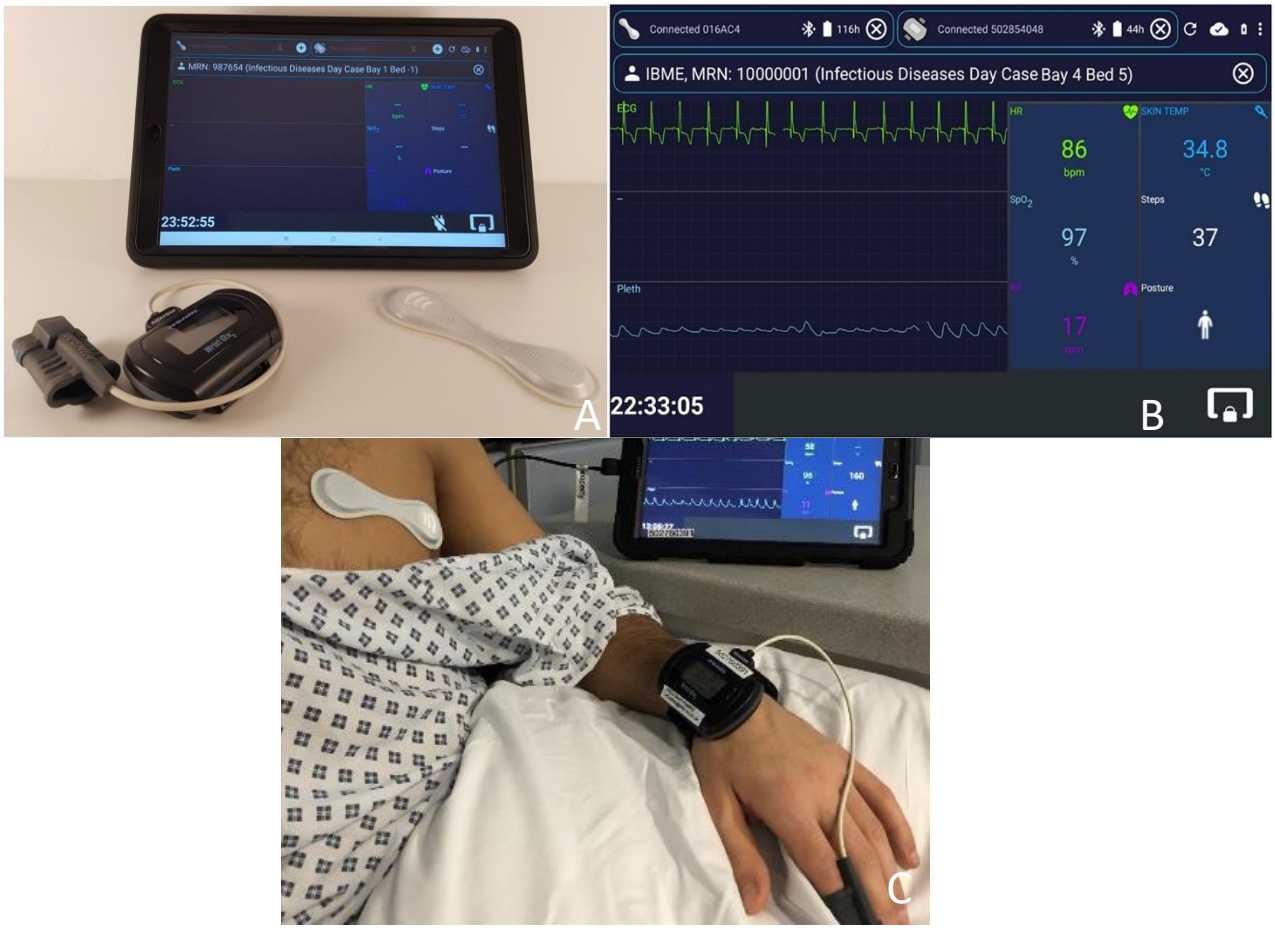


Figure 11 – A: Final vHDU kit per patient, including the Nonin pulse oximeter, the VitalPatch chest patch and an Android tablet, left inside the isolation rooms. B: Interface for patient data collection app in the Android tablet. C: Example of vHDU kit being worn inside room. IBME, Institute of Biomedical Engineering; MRN, Medical Record Number; bpm, beats per minute; rpm, respirations per minute; HR, Heart Rate; RR, Respiratory Rate; TEMP, Temperature; SpO2, peripheral blood Oxygen Saturation. Extracted from the published manuscript (CC BY 4.0) (Santos, M. D. et al. 2021, Morgado Areia et al. 2021).

The tablet would then transmit the collected wearables data via Wi-Fi to the hospital system, shown in our vHDU dashboard (Figure 12). In the dashboard homepage each patient was attributed a card, showing real-time vital sign and other patient and device information (Figure 12A). Clicking on a card

would display the augmented e-obs chart for the selected patient, displaying historical vital sign and EWS data at pre-set time periods (Figure 12B).

Figure 12 – A: vHDU dashboard, each card showing real-time vital sign data for each patient. B: vHDU e-obs chart for the selected patient. Extracted from the published manuscript (CC BY 4.0) (Santos, M. D. et al. 2021)

Deployment, feedback outcome and current status

The first patient was registered on the 23rd March 2020; and continuous support to the clinical staff was given by the research and engineering team throughout the pandemic. This included training on device calibration, connection and troubleshooting simple issues with the system.

Initial feedback on the system is explored in the manuscript (Santos, M. D. et al. 2021), with the VitalPatch being well-received by both nurses and patients, as it was easy to fit and connect. On the other hand, some patients found difficult to continuously wear the Nonin pulse oximeter, going in accordance with the wearability study results (**chapter 3**). Displaying the 4-hourly nurse observations alongside the wearables estimates in the Clinician Dashboard was also well-received by staff (Santos, M. D. et al. 2021).

The vHDU system has been used on/off throughout the pandemic and, as of 15 April 2021, a total 165 patients were monitored using our system, with 7752 total monitoring hours (approximately 323 days).

Future work

Future work will include the retrospective analysis of the vHDU data collected during the pandemic as, despite acknowledgement of the physical effects of COVID-19, little is known about the trajectory of vital signs for patients with this new condition (Pimentel et al. 2020). Our vHDU system implementation in clinical practice offers an opportunity to examine the patterns of vital signs which have been collected continuously over several days. This brings the potential to inform future management of this illness and other similar viral respiratory infections. Furthermore, as intermittent measurements of vital signs were also taken by staff using standard hospital equipment and based on local early warning score protocols, these data offer the opportunity to compare the use of continuous versus intermittent vital signs measurements to detect deterioration. Objectives/analysis are discussed in **chapter 7**.

Contribution to knowledge and originality

The manuscript in Frontiers in Digital Health was a timely addition to the limited literature on the use of wearable monitoring systems for remote patient monitoring during the pandemic:

1- It was an original piece of work implementing new technology as part of the covid response in a local hospital;
2- Although its implementation was fast to support clinical staff, the background work underpinning this was extensive (described in the previous chapters) allowing us to reassure staff and patients the system was ready and safe for use;
3- Provided important technical and practical implementation details of a WMS in the general ward environment;
4- Provided early data for other teams working in wearable remote covid patient monitoring;
5- Showcased other information on the training and education provided to the clinical staff for them to be able to use the vHDU system; an essential requirement for any successful deployment (Leenen et al. 2022a).

This paper was published in September 2021 and has been externally cited 10 times, using our system and deployment data in a wide range of research (Cheong et al. 2022, L. Poisson and O'Leary 2022, Alagumalai et al. 2022, van Goor et al. 2022, Kuo et al. 2022, Mejia, Rawal, and Rawat 2022, Pannase, Mahakalkar, and Gomase 2022, Uwamariya 2021, Chau et al. 2022, Martín Yeves 2022).

Reflection

This unprecedented pandemic opened the opportunity to deploy the vHDU system earlier than anticipated. Thanks to the effort from our research, engineering, and clinical teams, we managed to quickly integrate the selected devices, finalise the system and train clinical staff to use it in the COVID isolation wards. My contributions included supporting the design, testing, development, and refinement of the vHDU system; as well as all activities around the deployment of the WMS in the ward environment, such as stakeholders' awareness and engagement to support its implementation (IT, clinical governance and hospital management), clinical staff continuous training, support and assistance throughout the pandemic. It also included constant monitoring and feedback to ensure there were sufficient resources and the system was working properly.

Although there is still no strong evidence supporting the superiority of WMS, by adding the vHDU system to these wards in addition to standard care practices, our system potentially allowed not only to protect patients by promoting both their safety and mobility, but also the clinical staff, by reducing and/or prioritising their contact with infected patients. This was especially significant in the beginning of the pandemic, when the virality and severity of the virus was still unknown, personal protective equipment (PPE) was insufficient and guidance unclear (Scally, Jacobson, and Abbasi 2020). Deployment started in a single ward in the beginning of the pandemic, but with the rapid infection and death rises, ICU beds filling and hospital resources consumption, soon other wards were converted to COVID wards, and our WMS was requested throughout the hospital. This indicated the potential clinical support that WMS, such as our vHDU system, can provide as part of the hospital response in an emergency scenario.

Although there were some initial implementation challenges (such as clinical staff, management and other stakeholders' awareness of the system and training, technical infrastructure, system troubleshooting, among others) one important factor for the successful development and deployment of this system is our previous vHDU studies, which were crucial as:

- Prior selection of wearable devices (through studies explored in **chapter 1-4** and unpublished data) avoided the need for constant changes and iterations by nursing staff as devices/system was rapidly adopted.
- The VitalPatch was disposable, and Nonin easily sterilised, avoiding the risk of spreading.
- Use of interfaces familiar to the local clinical staff (using our qualitative study insights in **chapter 2**, and other unpublished qualitative interviews and focus groups data).
- Inclusion of fault-tolerant software mechanisms, such as automatically recover devices connection, avoiding staff entering the room to resolve.

- Rapid communication and feedback from the clinical to the research team, allowing swift iterations and improvement of the system throughout the pandemic.

This experience also provided some important lessons for our future work (**chapter 6**). Examples include (not limited to):

- The need for constant active involvement of all stakeholders (patients, clinical staff, management, and other relevant departments) before, during and after deployment.
- Providing the primary users of the WMS (staff and patients), constant support, training and continuously collecting their feedback to support future iterations of the system, ensuring it is fit for purpose.
- Adapting WMS implementation around current clinical care practices, minimising disruption during deployment.

In summary, this chapter outlines the process for the development and rapid implementation of the vHDU system as part of our local hospital clinical response to the pandemic. This was the result of years of testing and vHDU system development, discussed in the previous chapters, that was in a near-ready state for implementation when the pandemic occurred. Deployment data and lessons learnt supported the design of a local feasibility RCT, **chapter 6**.

Chapter 6:

Feasibility Randomised Controlled Trial Protocol

Context and objectives

The meta-analysis discussed in **chapter 1** highlighted the need for big and better clinical trials to assess whether WMS can impact deterioration detection and associated clinical outcomes (Areia, Carlos et al. 2021a). Therefore, a feasibility RCT was designed to assess the impact of the vHDU system integration (with active clinical alerts) versus standard care in deterioration detection. This trial will also explore other associated clinical outcomes, trial progression outcomes, staff impact, alerting system performance, overall system reliability and patient experience (Areia, Carlos et al. 2022). Since the COVID-19 deployment, the vHDU system has been augmented with the remaining vital signs: temperature (through the updated version of the VitalPatch) and a new Blood pressure cuff (A&D UA-1200 BLE device, A&D Medical, figure 13, therefore now monitoring all 5 vital signs continuously through the vHDU system. The objective of this feasibility trial is to put this updated version of the vHDU system to the test in surgical wards inside our local hospital, randomising 1:1 patients to either vHDU or standard monitoring care.

Figure 13 - A&D UA-1200 BLE blood pressure monitor.

P10: Feasibility randomised controlled trial

Submitted to Pilot and Feasibility studies journal (2022)	Pre-print (in review): Impact of an Ambulatory Monitoring System on Deterioration Detection and Clinical Outcomes in Hospitalised Patients. A Feasibility Randomised Controlled Trial Protocol. **Areia C**, Vollam S, Roman C, Santos M, Young L, Biggs C, Jarman A, Gerry S, Tarassenko L, Watkinson P.

Table 8 - Chapter 6 included pre-print.

Results (finalised protocol)

Both groups will be asked to use the vHDU system throughout their surgical ward length of stay (that includes the Nonin pulse oximeter, the VitalPatch chest patch, the A&D blood pressure cuff, and a tablet per patient). The difference between the intervention and control groups is that the clinical staff can access the dashboard data for the intervention group and will be alerted when they deteriorate. In the control group, patients will still be asked to wear the devices, but clinical staff will not have access to their data on the dashboard nor receive any alerts.

Up to 240 patients will be recruited and this feasibility RCT will include a calibration period for the first 50 patients, where we will finalise our alerting system (criteria and thresholds), according to the guidance highlighted in **chapter 1** and continuous clinical staff feedback. Outcomes are thoroughly described in the study protocol and include:

Primary:

1. Time from first period of unexpected physiological instability to set of observations

Secondary:

2. Other deterioration detection related outcomes
    - 2.1. Frequency and duration of physiological instability periods and nursing visits
    - 2.2. Time and frequency of unscheduled interventions
    - 2.3. ICU Admission
    - 2.4. Cardiac Arrest team call
    - 2.5. Complications and adverse events
    - 2.6. Control group only: Time difference between deterioration detection by nurse and AMS
3. Other clinical outcomes
    - 3.1. Mortality
        - 3.1.1. ICU mortality
        - 3.1.2. Hospital mortality
        - 3.1.3. 30-day mortality
    - 3.2. Length of stay (LOS)
        - 3.2.1. Ward LOS
        - 3.2.2. ICU LOS
        - 3.2.3. Hospital total LOS
4. Trial progression outcome

4.1. Recruitment rate

4.2. Patient and staff adherence

4.3. Outcome selection

4.4. Randomisation method and confounders

5. Staff impact and alerts

5.1. Proportion of false alerts and alert optimisation process during calibration period

5.2. Staff perception of the system

6. System reliability

6.1. Level of agreement between vHDU and manual EWS and individual vital signs

6.2. Frequency and duration of data drop-out for each vital sign parameter

6.3. Causes of system down-time

6.4. Waveform quality

6.4.1. VitalPatch Electrocardiogram waveform signal quality (used in HR and RR)

6.4.2. VitalPatch Accelerometer waveform signal quality (used in RR, Posture, Steps)

6.4.3. VitalPatch temperature waveform signal quality

6.4.4. Nonin Infrared Photoplethysmography waveform signal quality (used in SpO2 and PR)

7. Patient reported outcomes and experience

7.1. Patient Reported Outcome Measures (wearability questionnaire)

7.2. Patient compliance with wearable devices

7.3. Patient experience

Status

National ethical approval has been obtained by the Wales Research Committee 5 on the 24th August 2021 (reference 21/WA/0250). Trial successfully prospectively registered in ClinicalTrials.gov on the 12th November 2021 (ClinicalTrialsGov - NCT05118477). Recruitment started in August 2022.

Reflection

After the studies described in **chapters 1-5**, it is now time to put our system to the test in an unbiased environment. The need for robust RCTs is raised in the systematic review (Areia, Carlos et al. 2021a), and we are in an ideal position to conduct an initial local feasibility study. Then, if our progression criteria goals are met, data from this trial will be used to make a formal application for external funding for a multicentre RCT, with a thorough, data-based sample size calculation and an initial plan for the

number of sites/wards to be included. This is a long-term plan to hopefully provide the much-needed data and answer to my meta-analysis question (**chapter 1**).

In the protocol, I added three potential challenges that I feel needed to be discussed here. The first is the intrinsic bias of patient recruitment, as previous experiences (unpublished) indicate that the most likely population to consent for this trial are stable patients. During the design of the study, I considered other practical strategies to avoid this, such as:

- Discuss study with patients as soon as they are admitted to the ward;
- Approach straight after surgery, as soon as they regain capacity and remove the traditional continuous monitoring;
- Identify and approach patients in ICU about to be discharged to the trial ward;
- Include other wards receiving ICU patients;

The second challenge is that we are currently not including patients without capacity for this study. I believe this might be limiting our population, as patients under the Mental Capacity Act (MCA) may represent a significant percentage of the population of interest, and we might be biasing our results by not including them, when in fact these might be the ones needing it the most (more elderly, comorbidities, etc…). Although these are just assumptions, if we find this percentage is indeed high in the target wards, an amendment will be made to this protocol to request Confidentiality Advisory Group (CAG) permission to also recruit these patients.

The third potential challenge of this study might be the blinding of the control group data, as patients in this group will be encouraged to use the devices but will be blinded to its data. Clinical staff will also be blinded to this group's data and will not be alerted in case of a detected deterioration by the vHDU system. We foresee some challenges explaining the importance of the control group data blinding and will be conducting regular training sessions and 1:1 discussions with both staff and patients as necessary to improve consent and retention rates.

My work in the vHDU project made me aware of all the potential challenges when developing, testing, and deploying new technologies in clinical environments; and how simple practical things can serve as a confounder and bias trials such as these, also a reason for conducting a feasibility study before committing to a full trial. The pandemic deployment (**chapter 5**) taught me that there are a lot of operational, technical, and practical issues that only emerge after deployment, when we move the technology from the research (theoretical) to the clinical (practical) environment.

In summary, this protocol comprehensively outlines the methodological rationale and steps underpinning this feasibility RCT, that will hopefully provide not only robust clinical data, but also

operational insights so we can design a well-thought, multi-centre pragmatic RCT, that will give a fair trial at this technology to prove its worth.

Chapter 7

Critical Analysis

Narrative thread and final reflection

A conclusion from **chapter 1** was that despite the exponential growth of WMS, few studies are testing its implementation and clinical impact. Our previous work permitted to have the vHDU system in a "near ready-state" by the time the COVID-19 pandemic started; allowing us to finalise its development and quickly implement it in our local hospital. Our ability to quickly deploy a WMS inside the hospital during the pandemic supports the links between **chapters 1-4** in this synthesis, as several factors contributed to its rapid and successful implementation:

a) Comprehensive understanding of current WMS clinical impact evidence (**chapter 1**) and local monitoring practices and protocols (**chapter 2**):

The systematic review and meta-analysis provided important practical information on current available devices capabilities, implementation challenges and system iterations with clinical staff. An example would be the need to focus on actionable alerts. In **chapter 1**, all studies with alerting systems focused their efforts in reducing artifacts and false alerts, by frequently going to the wards, liaising, and collecting feedback with clinical staff and individualising thresholds by adjusting the system to that particular patient (Weller, Foard, and Harwood 2018, Skraastad et al. 2020, Downey, C. et al. 2018, Downey, C L et al. 2018, Weenk et al. 2020, 2019). This was also described in **chapter 2**, where both nurses and patients agreed WMS should not add more noise to the ward, as that will contribute even further to the already existing alarm fatigue by the nursing staff (Areia, Carlos et al. 2021b). Furthermore, excessive alarms can have a detrimental effect towards the system as it becomes challenging for staff respond to the alerts, with other external factors also playing a role, such as staff capacity and workload (Leenen et al. 2022a, Prgomet et al. 2016). There is also evidence that it may cause distress and anxiety to patients, leading to more time spent from the clinical staff to reassure them (van Loon et al. 2015, Downey et al. 2022).

The qualitative interviews provided further crucial guidance in the implementation of the vHDU system, by understanding current monitoring practices and early clinical staff and patient views on potential impact of WMS integration in clinical care. We tried to build our system using the current practice knowledge acquired from this qualitative data and other (unpublished) focus groups throughout the project.

b) Selection of wearable devices with clinically acceptable wearability (**chapter 3**) and accuracy (**chapter 4**):

Since the beginning of the project, we prioritised the need for a thoughtful balance between wearability and accuracy. In **chapter 2**, nurses highlighted that traditional continuous monitoring was not applicable to all patients, and could be disruptive if they wanted to mobilise, often resulting in the removal of the monitoring cables. This reinforced the need of the wearability study described in **chapter 3** and was one of the main reasons why we started by testing devices comfort before even submitting them to accuracy testing (**chapter 4**).

"*It doesn't matter how great a device is if patients don't wear it."* – Nurse feedback during a focus group (unpublished)

The work in **chapter 1** also highlighted current concerns around devices accuracy, supporting the need for an internal validation study (**chapter 4**) before moving them to the hospital environment. After this, data was collected on both devices' wearability and accuracy, that allowed us, together with the clinical staff, to make an informed and prompt decision on which devices would be integrated into the WMS to monitor isolated COVID patients (**chapter 5**). For example, the Wavelet was the clear favourite pulse oximeter, due to the lack of a finger probe, however it failed our accuracy tests. The second preference was the CheckMe O2+, as a more user-friendly finger probe, that does not compress the fingertip, with clinically acceptable accuracy results, not implemented during the pandemic only due to some practical challenges (explored in **chapter 5**); being the selected pulse oximeter the Nonin. This was reflected in the total worn time by patients in our wearability study, so I suspect worn times would probably be much higher if the Wavelet or CheckMe were the ones used during COVID deployment. Future companies should focus their efforts in developing a long-battery lasting, accurate pulse oximeter with a user-friendly finger probe, or without one at all.

The diagnostic accuracy testing during movement and controlled hypoxia reassured staff and COVID-19 patients in the isolation wards that all included finger worn pulse oximeters were able to detect hypoxaemia, excluding the only wrist worn Wavelet device (Santos, M. et al. 2021). It also provided information on potential movements that could degrade performance (for example rubbing or tapping the finger probe). I believe these results were able to encourage patient mobility whilst in isolation, knowing they were still being continuously monitored. The VitalPatch HR and RR validation analysis also reassured staff and patients that its performance was not affected by most movements and moderate to severe hypoxia (as it was common for covid patients to suddenly desaturate (Morgado Areia et al. 2021)).

c) Continuing involvement and collaboration with clinical staff, hospital departments and management (**chapter 2-5**)

As a result of the ongoing vHDU project work and communication with the multiple departments involved, the vHDU system was quickly iterated and finalised with the clinical staff. By using a familiar user interface, with minimal training, nursing staff when making their observations were able to review the outputs of the data collection app on the Android tablet as if it were a "bedside monitor" (Figure 11A and 11B). Additionally, the charts on the remote Clinician Dashboard (Figure 12A and 12B) were modelled on those used in the electronic observation system, already widely used throughout the hospital (Santos, M. D. et al. 2021). We also made every effort to ensure the system could recover automatically from disconnection and other issues, with me and my colleagues continuously present in the isolation wards throughout the pandemic, minimising the need for technical troubleshooting from clinical staff. Using the close collaborations between researchers, engineers, clinical staff, and other hospital teams facilitated the continuous feedback and iterations throughout the pandemic; continuously improving our system (Santos, M. D. et al. 2021).

According to our results throughout the vHDU project (Areia, Carlos et al. 2021a, Xu et al. 2021, Areia, Carlos et al. 2021b) and other research (Leenen et al. 2022a, 2020, Sun et al. 2020), although wearable technology is exponentially growing, there is still uncertainty around their accuracy (Xu et al. 2021) and potential impact on patient safety (Areia, Carlos et al. 2021a); therefore these devices and systems should be tested and implemented as a complement, and not a substitute, to standard care and direct patient contact (Xu et al. 2021, Areia, Carlos et al. 2021b). It should also not disrupt normal care pathways, for example not using WMS as the reason to discharge a patient earlier from ICU, as it might result in higher nursing workload and unsafe care (Leenen et al. 2022a). Using the lessons learnt from this deployment (**chapter 5**) and the information gathered throughout the vHDU studies, we have now designed a feasibility RCT (**chapter 6**) to put our system to the test against standard care. Besides assessing the impact of the vHDU system in deterioration detection and associated clinical outcomes in our local hospital it will also evaluate the feasibility of a definitive RCT, this trial will support the sample size calculation for the full study, assess the recruitment and retention rate and the need for inclusion of other wards and other sites. Clinical staff and patient interviews and focus groups will continue to be held for further refinement and improvement of the vHDU system, in particular to the alerting system (Areia, Carlos et al. 2022).

Overall contribution to the field

The vHDU studies were used for my doctoral portfolio as I strongly believe this project outlines a robust pipeline from its concept to implementation. To my knowledge, although several research teams and industry companies are developing and testing these medical devices and WMS, the vHDU project is the first to transparently publish all the involved process to its deployment as part of the local clinical response to the pandemic. Each step of this project has made significant individual contributions to the field of wearable healthcare monitoring and is outlined in the respective chapter. As described throughout this synthesis, all chapters and publications are inter-related (Appendix 1), and often self-cited throughout the publications (citation network in Figure 14).

Figure 14 – Journals citation network, BMJ Open (P1 and P6), Critical Care (P2 and P3), Frontiers in Digital Health (P9), JMIR (P6 and P7), JMIR mHealth and uHealth (P5), Journal of Advanced Nursing (P4), Research Square (P10). Figure downloaded from Dimensions website (Hook, Porter, and Herzog 2018).

The biggest contribution of this synthesis is the pipeline and thread created throughout the vHDU studies. This progressive work provides evidence and information not only on technical aspects (such as accuracy and reliability assessment, system integration and deployment) but also on the human factors surrounding our work. The interview and focus group qualitative data have been central throughout this project, reiterating the importance of mixed-methods approach to this type of work (Palinkas et al. 2011, Creswell and Plano Clark 2011), that proved to be crucial in the implementation process during an unprecedented global emergency.

Overall, I believe my own contributions through this work also open multiple pathways to further external research and provide important information on the steps in the development and

deployment of wearable systems in the hospital environment, that can be of use to organisations and clinical entities. Using wearables for remote monitoring have the potential to promote safety and early deterioration detection, as well as improve clinical outcomes, and I believe we are not far from this technology to be part of hospital care, however, research needs to continue to ensure its integration is appropriate, by reducing care disruption and maximising its usefulness to all stakeholders.

As this work was funded by the NIHR Oxford Biomedical Research Centre, all the included outputs are fully open access, meaning they can be easily and freely accessible to everyone interested in this work. All manuscripts are published in journals in the top quartile of their respective field, from clinical engineering, nursing, and critical care. With ranging impact factors from 2.692 to 9.097, indicating that all papers have been through several rounds of peer review and iterations before being published, supporting the methodological quality of this doctoral work.

Overall limitations

Limitations of each paper are described inside the respective manuscript. This doctoral work also has its limitations. Firstly, due to the pandemic, the vHDU project had to stop in the general wards, which was also a strength as we focused our efforts on finalising and deploying the system in the covid isolation wards, accelerating the development of the vHDU system. This re-focus considerably delayed/cancelled the publication of other studies of this project (such as locational testing, user interface development qualitative work, vital sign reliability surveys, among others, all unfinished or unpublished). However, I strongly believe the included outputs are the main body of work underpinning our vHDU project and this doctoral thesis.

Recommendations and future work

A clear plan needs to be developed by everyone involved on how best to harness this WMS technology while integrating it into hospital care. Firstly, as already discussed, I am a strong advocate that initial integration of WMS should always be as a complement and not a replacement to standard care (Xu et al. 2021). Secondly, WMS needs to be optimised as much as possible before deployment, and should not be disruptive of practices and protocols, to avoid resistance from staff, patients and other stakeholders, ending in early technology failure (Taenzer et al. 2011). It should also consider all the human factors surrounding its implementation and involve clinical staff and patients in its design from the very beginning, to ensure systems are user-friendly, and are capturing and doing what staff and patients need (Lewy 2015). Finally, I also believe that this technology is not applicable to all environments and populations, so careful thought and discussions should be held before considering its integration, to promote, or even welcome, its use and acceptance (Smuck et al. 2021, Downey et al. 2022).

"*Implementation of these technologies requires the collaboration of the healthcare professionals and patients, not just in adoption, but also in the process of development and implementation in best practice and care pathways."* (Lewy 2015)

Not only the technology needs to be ready for clinical use, but also its end users need to be prepared, as another important aspect of successful integration is appropriate staff training and education. Due to several individual, organisational, and educational factors, there is overall lack of knowledge on data interpretation, trend analysis and wearable technology knowledge by clinicians (Smuck et al. 2021). To support the rollout, testing, and training of WMS, perhaps the use of clinical champions to support its deployment may increase the likelihood of its success. In the vHDU case, we kept strong relationship with clinical staff throughout the project, and quickly built new ones with staff in the isolation wards, with support from senior staff and Practice Development Nurses (PDNs).

A potential real positive impact from WMS could also be its integration into hospital systems, as automatic real-time continuous monitoring may reduce the time spent on vital sign measurement and manual recording into electronic systems (Redfern et al. 2019, Dall'Ora et al. 2019, 2021) and improve staff workload and productivity (Leenen et al. 2022a, Areia, Carlos et al. 2021b). The vHDU system was developed with the long-term of hospital system integration, however, during the feasibility and testing, this system is only extracting data from the EPR and SEND (Wong et al. 2015) systems. Another potential feature that we will perhaps explore in the future how to best incorporate nurses concern into the vHDU system; I strongly believe the "nurse worry factor" to be a very powerful tool, especially when a patient is deteriorating without physiological decline of their vital signs (as highlighted in **chapter 2**), with several studies supporting its use (Odell, Victor, and Oliver 2009, Douw et al. 2016, Mok, Wang, and Liaw 2015, van Rossum et al. 2021), and even suggesting it can outperform standard EWS (Romero-Brufau et al. 2019).

With all these challenges and future work in mind, our next step is the feasibility RCT discussed in **chapter 6**, with the long-term objective of acquiring independent funding for a full, multicentre RCT, that will hopefully fill the gap highlighted in the meta-analysis (**chapter 1**). I envisage this work to potentially provide robust data on the impact of WMS in the deterioration detection and associated clinical outcomes, that will likely contribute to the future of clinical monitoring and healthcare practice. As of the 5th November 2022, the feasibility RCT is ongoing, currently recruiting patients.

Other analyses are being finalised and several other studies/ideas emerging from the work outlined in this synthesis being explored (Table 9):

Table 9 – Future research studies and ideas resulting from the vHDU project.

Resulted from chapter	**Study**	**Status**
2	Clinical staff survey on the perceived reliability of current vital sign monitoring methods used in the hospital environment	Writing
2 & 5	Clinical staff survey on the perceived reliability of current vital sign monitoring methods versus vHDU system in the COVID wards	Writing
2 & 5	Qualitative interviews and focus groups analysis during VHDU system development and COVID-19 deployment	Writing
5	Retrospective analysis of vital signs data from patients with COVID-19 using the 'virtual high dependency unit' monitoring system. Objectives will include: a) Describe the physiological pattern of vital signs over the course of COVID-19 infection for hospitalised level 1 patients. b) Compare detection of clinical deteriorations in continuous ambulatory monitoring of vital signs with deteriorations detected through intermittent vital signs measurements. c) Assess the number of adverse events in COVID-19 patients monitored via the vHDU system. d) Define antecedents to adverse events detected in continuous vital signs data, compared with patients without an event. e) Measure the agreement between vHDU system and nurse manual vital-sign measurements. f) Measure vHDU system reliability	Data analysis
6	Impact of the vHDU system on deterioration detection and clinical outcomes in hospitalised patients. A feasibility randomised controlled trial (**chapter 6**)	Ongoing
2 & 6	Qualitative interviews and focus groups analysis during alerting system iterations and feasibility RCT	Ongoing
Resulted from chapter	**Idea**	
3	Develop scale for patient perceived comfort, wearability and safety of medical wearable devices and/or WMS.	
4	Pulse oximetry accuracy differences in different skin colour types (using the hypoxia study data).	
6	Full randomised controlled trial.	

Other applications of the technology and contributions not explored in this synthesis

Besides the general ward, this or similar technology has the potential to promote patient safety in other settings as well, such as care/nursing or the patient's own home. The COVID19 pandemic has boosted the growth of remote clinical monitoring in order to reduce admissions to hospital and ED attendance, promote stable patients' self-management and reduce readmissions and overall

healthcare system capacity through the use of remote monitoring tools (Gruwez et al. 2022, Bouabida et al. 2021, Pronovost, Cole, and Hughes 2022, Fan et al. 2021). Simultaneously to the vDHU project, our team was also collaborating with the Nuffield Department of Primary Care Health Sciences and developing hospital to home studies using similar monitoring technology in neck of femur fractures (Armitage et al. 2020, 2021), COPD (Whelan et al. 2021) and hypertension (Armitage et al. 2019) patients. I was also involved in another study testing the feasibility and accuracy of video-based non-contact vital sign monitoring by mapping the lower limb skin perfusion using a camera (Harford et al. 2020).

These are just some examples of the panoply of fields and environments remote monitoring technology can support; with several other healthcare applications that appropriate WMS integration can potentially benefit.

Contributorship statements

All authors contributions as well as my own are outlined in the "author contribution" section of each respective manuscript. In **chapter 1**, I conducted the systematic review and meta-analysis, from research question design, protocol development, PROSPERO registration, protocol publication, study selection, bias assessment, statistical analysis, manuscript writing, journal submission, peer review response and letter response to editor. In **chapter 2**, I was responsible for qualitative data analysis, manuscript writing and peer review response. In **chapter 3** I was responsible for data analysis, manuscript writing, journal submission and peer review response. For **chapter 4** publications, I led the protocol development and its publication (P6), managed regulatory approvals and amendments, led the study during recruitment and data collection period, designed and analysed the data for the chest patch validation study (P7), and was responsible for the respective journal submissions and peer reviews. In **chapter 5**, I supported the design and testing of the vHDU system, implementation in the COVID wards, reviewed and approved the final manuscript. Finally, in **chapter 6**, I collaborated with the team to design the feasibility clinical trial (in peer review) and was responsible for the protocol development and acquiring relevant national and local regulatory approvals.

Research career, skill development and growth throughout project

As the vHDU project progressed, I progressively developed as a researcher with it, and have grown from collaborating and supporting studies to design and lead my own (table 10).

Study activity contribution	**Chapter 1**			**2**	**3**	**4**			**5**	**6**
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**
Research question design										
Protocol development										
Research ethics application										
Registered PROSPERO										
Designed search strategy/terms										
Selected studies for inclusion										
Data extraction										
Quality and bias assessment										
Recruitment									*	
Data/statistical analysis										
Initial manuscript draft										
Final approval of manuscript										
Peer review response										

*Table 10 – Contributions table. Green: main responsible/lead, Yellow: supported, Red: not contributed, Grey: Not applicable. * Note: In P9 refers not to the recruitment of research participants but implementation of the vHDU system in the clinical wards.*

Chapter 1 was the first systematic review that I designed and led from conception to publication. It highlights the transparency I envisaged for the vHDU project at the time, by registering it early in PROSPERO and publishing the protocol. This was a lengthy and laborious review, with over 18 months of work and 8706 citations manually reviewed by me and another colleague. It made me appreciate the multidisciplinary effort and all the background work that is necessary to produce a methodologically robust review. It was also the first time I conducted a meta-analysis, that greatly developed my statistical knowledge.

In **chapter 2**, it was my first experience in applied qualitative research, allowing me to develop and apply thematic analysis principles (Braun and Clarke 2006, 2013). I now understand how demanding qualitative research is, and how methodical thematic analysis needs to be to create robust qualitative insights. Despite its challenges, all this work raised my own awareness to the importance of mixed-methods research in digital health, and how crucial it was to promptly deploy the vHDU system during COVID.

Chapter 3 was my introduction to programming and statistics, for the first time, I designed and conducted the statistical analysis using R and RStudio. This is where I discovered my passion for data analytics and my development journey in this field began. Soon after, I joined a postgraduate course in Health Data Analytics at UCL. In **chapter 4**, the chest patch validation required more advanced statistics, and this challenge further progressed my skills in time series and big data analysis, with the support of my engineering colleagues. I am now pursuing a full-time career in data science.

Chapter 4 was one of the most operationally challenging studies I have ever conducted, however, it allowed me to develop my organisational and project management skills. As mentioned in this chapter, by leading the day-to-day activities of this experiment, I had to manage a multitude of variables to ensure everything was running smoothly, from facilities, resources, kit, participants, and my own team. Although challenging, this also developed several of my leadership skills, such as conflict resolution, motivational management and work ethics.

Chapter 5 outlines probably the most thrilling time of my career, that was simultaneously scary and exciting, contributing not only to my professional, but also personal development. As a researcher there is nothing as fulfilling to see our work being rapidly translated into clinical practice in a worldwide emergency, supporting patients and staff during its deployment and seeing its impact in real time. It is in these situations that one quickly realises that all the work and dedication was surely worth it, and how important robust research is.

Finally, **chapter 6** converges my previous work in the design of a feasibility clinical trial. My previous experiences made me aware of all the challenges when developing, testing, and deploying new technologies in clinical environments; and how simple practical things can serve as a confounder and bias trials such as these, also a reason for conducting a feasibility study before committing to a full trial. The pandemic deployment taught me that there are a lot of operational, technical, and practical issues that only emerge after deployment, when we move the technology from the research (theoretical) to the clinical (practical) environment. Hopefully, this study will provide not only robust clinical data, but also operational insights so we can design a well-thought, pragmatic RCT, that will give a fair trial at this technology to prove its worth.

There is an immense collaborative effort behind the work outlined in this synthesis. Besides the multi-professional research group from diverse departments within the University of Oxford, I have also closely collaborated with multiple industry partners and local hospital departments (such as clinical engineering, IT, clinical governance, amongst many others). This allowed me to build a solid network of colleagues throughout these publications (Figure 15).

Figure 15 – Researchers network from included publications. Note: network limited to included studies. Extracted from Dimensions software (Hook, Porter, and Herzog 2018)

The vHDU project greatly contributed to my development as clinical academic, as I feel fully capable to lead studies through their life cycle, from protocol development, ethical submissions, project management, data analysis, to publication and dissemination. Besides, I also feel confident in leading different types of research, such as systematic reviews, qualitative, quantitative (observational, diagnostic, interventional and RCTs) and mixed-methods studies. More importantly, this project taught me to see the several components of research as a whole and think about the big picture.

The first publication from this thesis was published in early 2020, with the last still in peer-review (submitted February 2022). All 10 outputs included a total of 52 citations, with a mean of 5.2 citations per article (Figure 16). In the past couple of years my vHDU work has also been mentioned 159 times on Twitter, 2 on Facebook, 4 in news, 1 in blogs, 3 in peer reviews (Figure 17). Whenever possible, I tried to publish the study protocol for methodological transparency, and the work on this project made me realise my position as an advocate of “open access” research.

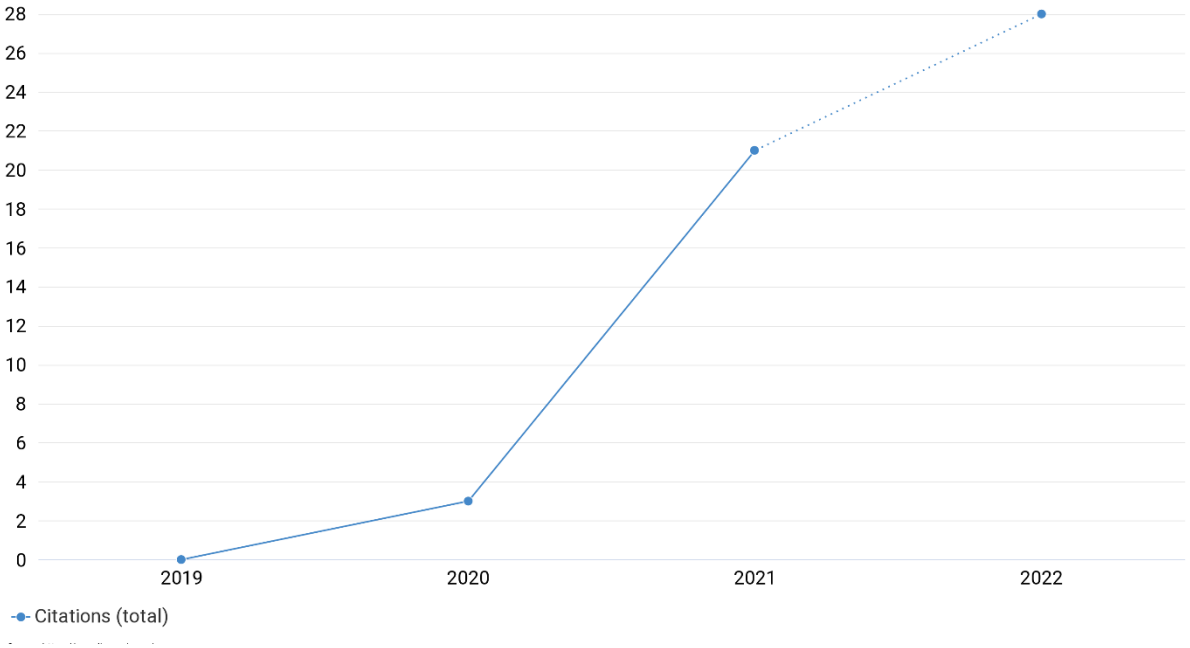


Figure 16 –Citations from publications included in this synthesis as of 05th November 2022. Extracted from Dimensions software (Hook, Porter, and Herzog 2018). *Solid line refers to complete years (2019, 2020 and 2021) and dotted line the current year (November 2022).*

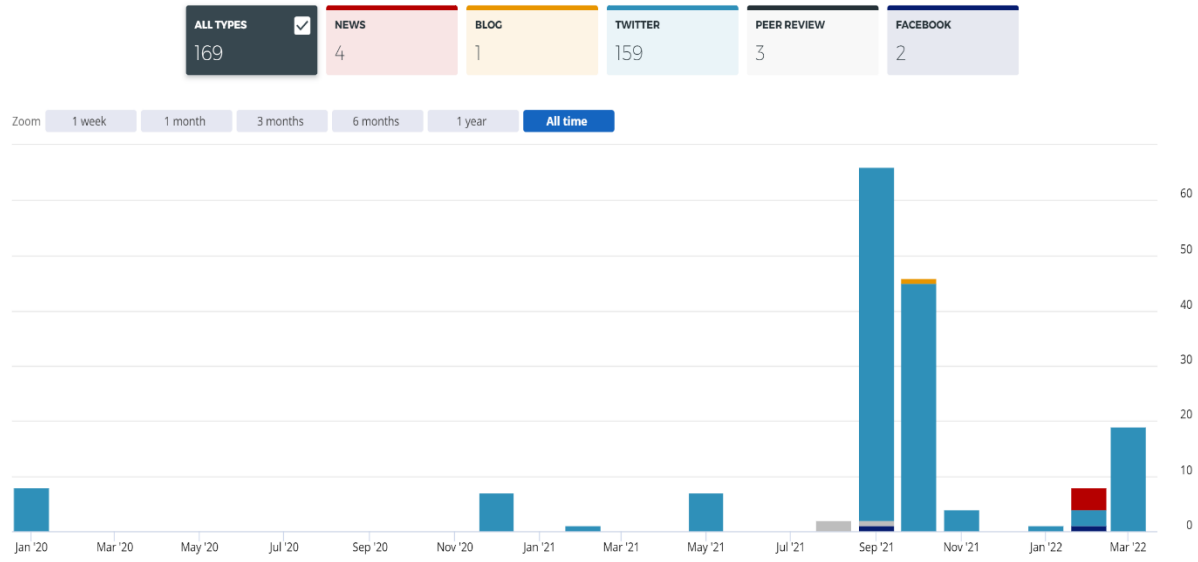


Figure 17 – Historical social media mentions from publications included in this synthesis as of 05th November 2022. Extracted from Altmetric software (Digital Science 2022).

I have also showcased some of my vHDU project work in national and international conferences in the past few years, from allied health professional to critical care themed conferences. There I have presented posters (Areia, C et al. 2022b, 2020), rapid (Areia, C et al. 2022a, 2021, Areia et al. 2019b) and platform presentations (Areia, C et al. 2022c). I believe this dissemination work was important to reach other academics, clinicians and promote public awareness of remote wearable monitoring capabilities and developments.

Furthermore, I am also an advocate for health data science and analytics skills for nurses and allied health professionals, providing support and teaching whenever possible. I have been an Associate Lecturer at Oxford Brookes University since 2021, and recently tutored 2 MSc thesis to completion at Oxford Brookes University, with the themes:

A) "A Systematic Review and Meta-Analysis Investigating the Effects of mHealth Exercise Interventions in Relation to a Comparator for Individuals with Type 2 Diabetes Mellitus (T2DM)."
B) "The effectiveness of wearable devices on pressure ulcer prevention compared to standard care: a systematic review, meta-analysis and narrative analysis."

In summary, my work on the vHDU knowledge allowed me to develop, among many others, my research, organisational and leadership skills and establish myself as an academic in the field of wearable monitoring. It also allowed me to find my passion for data analytics that I am now pursuing as a career alongside clinical and research work. This doctoral degree will hopefully open the door to future opportunities of independent funding and leadership.

Conclusion

This doctoral synthesis showcases the work and impact of the vHDU project through its multiple studies, from evidence gap identification on the impact of WMS, to wearables devices selection and testing, WMS development and deployment during the COVID-19 pandemic, and design of a randomised trial, that circles back to the first stage, with the aim of providing scientific evidence on the impact of our WMS (vHDU system) in deterioration detection and associated clinical outcomes. Besides highlighting each study and overall project contributions to knowledge, this synthesis also emphasised my own contributions to the field of wearable healthcare monitoring, as well as my development and growth as a clinical researcher from a supporting/coordination role to designing, managing, and leading my studies within this project.

The contributions of this synthesis and my work within this project are numerous, that range from thorough methodological and reproducible published protocols widely available to the public, to providing mixed-methods data on the existing state of evidence in the field, current local monitoring experiences by local staff and patients, devices wearability, validation and diagnostic accuracy, detailed WMS development and implementation data during COVID-19, and finally, how all this work will converge in a clinical trial. The novelty of this work does not only open the door to a wide range of other studies, but also provides important lessons learnt and other data that will support fellow colleagues in their own research. Hopefully, this project and my future work in the field will keep supporting the development, testing, and integration of appropriate wearable healthcare monitoring technology in the hospital environment, improve patient safety and perhaps even help shaping the future of healthcare.

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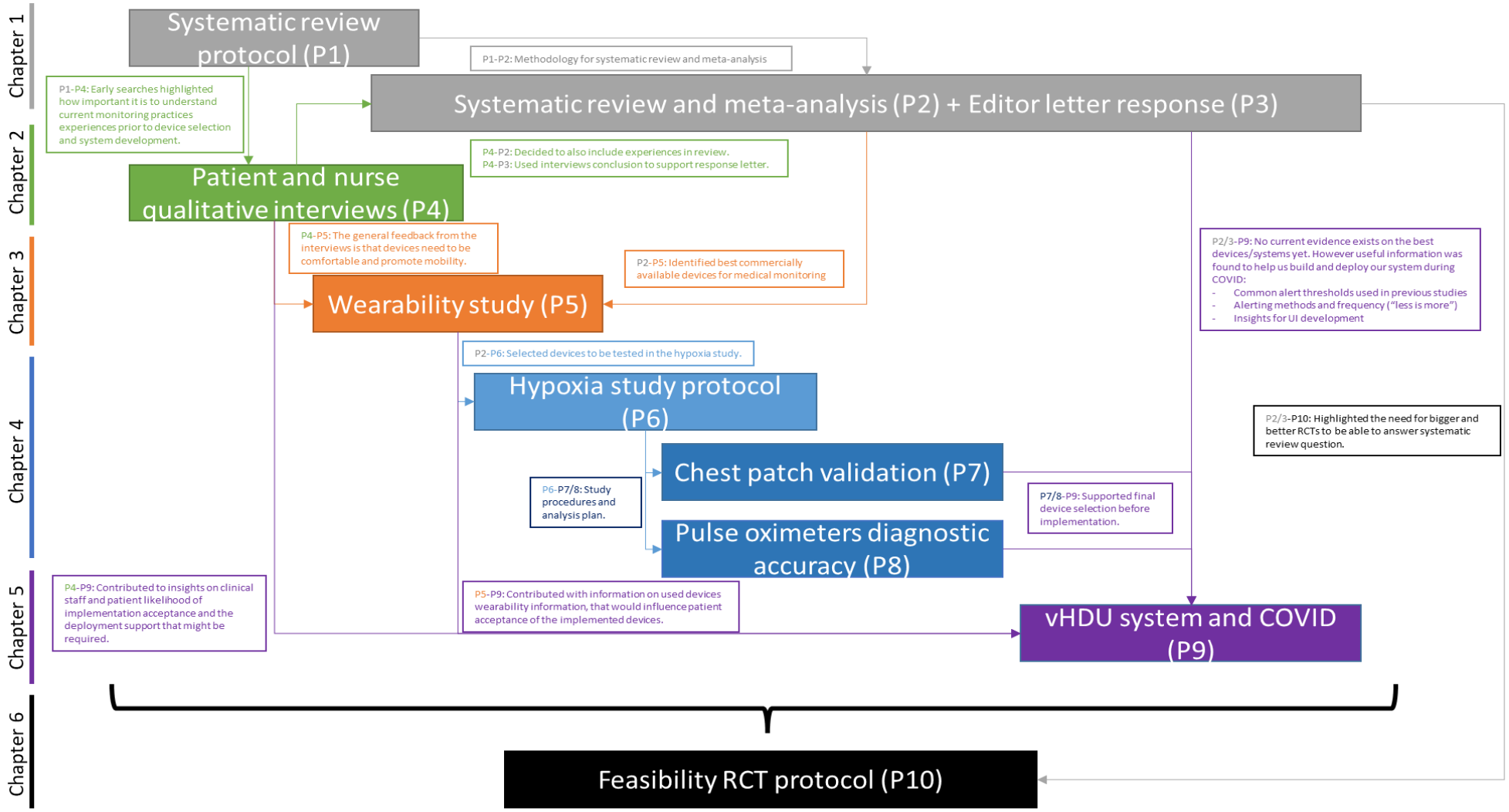
Appendix 1- Relationship flowchart



Appendix 2- Candidate full publication list

2.1- Included publications

1 Areia C, Vollam S, Young L, et al. Protocol for a systematic review assessing ambulatory vital sign monitoring impact on deterioration detection and related clinical outcomes in hospitalised patients. BMJ Open 2021;11. doi:10.1136/bmjopen-2020-047715

2 Areia C, Biggs C, Santos M, et al. The impact of wearable continuous vital sign monitoring on deterioration detection and clinical outcomes in hospitalised patients: a systematic review and meta-analysis. Critical Care 2021;25:351. doi:10.1186/s13054-021-03766-4

3 Xu W, Gharibans AA, Bissett IP, et al. Continuous wireless postoperative monitoring using wearable devices: further device innovation is needed. Critical Care 2021;25:394. doi:10.1186/s13054-021-03805-0

4 Areia C, King E, Ede J, et al. Experiences of current vital signs monitoring practices and views of wearable monitoring: A qualitative study in patients and nurses. Journal of Advanced Nursing 2021;n/a. doi:https://doi.org/10.1111/jan.15055

5 Areia C, Young L, Vollam S, et al. Wearability Testing of Ambulatory Vital Sign Monitoring Devices: Prospective Observational Cohort Study. JMIR Mhealth Uhealth 2020;8:e20214. doi:10.2196/20214

6 Areia C, Vollam S, Piper P, et al. Protocol for a prospective, controlled, cross-sectional, diagnostic accuracy study to evaluate the specificity and sensitivity of ambulatory monitoring systems in the prompt detection of hypoxia and during movement. BMJ Open 2020;10:e034404. doi:10.1136/BMJOPEN-2019-034404

7 Areia C, Santos M, Vollam S, et al. Chest patch for continuous vital-sign monitoring: A clinical validation study during movement and controlled hypoxia. Journal of Medical Internet Research 2021;in press. doi:10.2196/27547

8 Santos M, Vollam S, Pimentel M, et al. Wearable pulse oximeters in the prompt detection of hypoxaemia and during movement: a diagnostic accuracy study. Journal of Medical Internet Research (JMIR) Published Online First: 2021. doi:21/03/2021:28890

9 Santos MD, Roman C, Pimentel MAF, et al. A Real-Time Wearable System for Monitoring Vital Signs of COVID-19 Patients in a Hospital Setting. Frontiers in Digital Health 2021;3:120. doi:10.3389/fdgth.2021.630273

10 Areia C, Vollam S, Roman C, et al. Impact of an Ambulatory Monitoring System on Deterioration Detection and Clinical Outcomes in Hospitalised Patients. A Feasibility Randomised Controlled Trial Protocol. Pre-print: submitted to Pilot and Feasibility Studies journal Published Online First: 2022. doi:10.21203/rs.3.rs-1191653/v1

2.2- Publications not included but related

11 Armitage LC, Chi Y, Santos M, et al. Monitoring activity of hip injury patients (MoHIP): a sub-study of the World Hip Trauma Evaluation observational cohort study. Pilot Feasibility Stud 2020;6:1–11.

12 Whelan M, Biggs C, Areia C, et al. Recruiting patients to a digital self-management study whilst in hospital for a chronic obstructive pulmonary disease exacerbation: A feasibility analysis. Digital Health 2021;7:20552076211020876.

13 Harford M, Areia C, Villarroel M, et al. Study protocol for an exploratory interventional study investigating the feasibility of video-based non-contact physiological monitoring in healthy volunteers by Mapping Of Lower Limb skIn pErfusion (MOLLIE). BMJ Open 2020;10:e036235.

2.3- Posters and presentations

14 Areia C, Jarman A, Biggs C, et al. Vital sign monitoring methods and perceived reliability differences between physiotherapists and nurses. A cross-sectional survey study. Physiotherapy 2022;114:e60–1. doi:10.1016/j.physio.2021.12.316

15 Areia C, King E, Young L, et al. Patient and nurse experience of vital-sign monitoring practices and preliminary views of wearable monitoring: Qualitative study in a surgical ward. Physiotherapy 2022;114:e223. doi:10.1016/j.physio.2021.12.212

16 Areia C, Vollam S, Ede J, et al. Regulatory challenges of designing and testing continuous ambulatory vital signs monitoring in ward environments: lessons learned from the vHDU project. Physiotherapy 2020;107:e128. doi:10.1016/j.physio.2020.03.185

17 Areia C, Vollam S, Santos M, et al. The future of vital sign monitoring: Testing and comparing ambulatory monitoring devices accuracy and wearability. Physiotherapy 2021;113:e159. doi:10.1016/j.physio.2021.10.160

18 Armitage L, Chi Y, Santos M, et al. Monitoring activity of Hip Injury Patients (MoHIP): A sub-study of the World Hip Trauma Evaluation Observational Cohort Study. Physiotherapy 2021;113:e145–6. doi:10.1016/j.physio.2021.10.140

19 Areia C, Santos M, Vollam S, et al. Chest patch for continuous vital-sign monitoring: A clinical validation study during movement and controlled hypoxia. Physiotherapy 2022;114:e4. doi:10.1016/j.physio.2021.12.244

2.4- Other publications

20 Beard DJ, Davies L, Cook JA, et al. Rehabilitation versus surgical reconstruction for non-acute anterior cruciate ligament injury (ACL SNNAP): a pragmatic randomised controlled trial. The Lancet 2022;400:605–15.

21 Lai LYH, Arshad F, Areia C, et al. Current Approaches to Vaccine Safety Using Observational Data: A Rationale for the EUMAEUS (Evaluating Use of Methods for Adverse Events Under Surveillance-for Vaccines) Study Design. Front Pharmacol 2022;13:554.

22 Kostka K, Duarte-Salles T, Prats-Uribe A, et al. Unraveling COVID-19: a large-scale characterization of 4.5 million COVID-19 cases using CHARYBDIS. Clin Epidemiol 2022;14:369.

23 Williams RD, Markus AF, Yang C, et al. Seek COVER: using a disease proxy to rapidly develop and validate a personalized risk calculator for COVID-19 outcomes in an international network. BMC Med Res Methodol 2022;22:1–13.

24 Morales DR, Ostropolets A, Lai L, et al. Characteristics and outcomes of COVID-19 patients with and without asthma from the United States, South Korea, and Europe. Journal of Asthma 2022;:1–11.

25 Reyes C, Pistillo A, Fernández-Bertolín S, et al. Characteristics and outcomes of patients with COVID-19 with and without prevalent hypertension: a multinational cohort study. BMJ Open 2021;11:e057632.

26 Prats-Uribe A, Sena AG, Lai LYH, et al. Heterogeneity and temporal variation in the management of COVID-19: A multinational drug utilisation study including 274,719 hospitalised patients from, the United States of America, China, Spain, and South Korea. Pharmacoepidemiol Drug Saf 2021;:78–9.

27 Li X, Lai LYH, Ostropolets A, et al. Bias, precision and timeliness of historical (background) rate comparison methods for vaccine safety monitoring: an empirical multi-database analysis. Front Pharmacol 2021;:3307.

28 Recalde M, Roel E, Pistillo A, et al. Characteristics and outcomes of 627 044 COVID-19 patients living with and without obesity in the United States, Spain, and the United Kingdom. Int J Obes 2021;45:2347–57.

29 Roel E, Pistillo A, Recalde M, et al. Characteristics and outcomes of over 300,000 patients with COVID-19 and history of cancer in the United States and Spain. Cancer Epidemiology, Biomarkers & Prevention 2021;30:1884–94.

30 Duarte-Salles T, Vizcaya D, Pistillo A, et al. Thirty-day outcomes of children and adolescents with COVID-19: an international experience. Pediatrics 2021;148.

31 Prats-Uribe A, Sena AG, Lai LYH, et al. Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study. BMJ 2021;373.

32 Reps JM, Kim C, Williams RD, et al. Implementation of the COVID-19 vulnerability index across an international network of health care data sets: collaborative external validation study. JMIR Med Inform 2021;9:e21547.

33 Tan EH, Sena AG, Prats-Uribe A, et al. COVID-19 in patients with autoimmune diseases: characteristics and outcomes in a multinational network of cohorts across three countries. Rheumatology 2021;60:SI37–50.

34 Reps JM, Kim C, Williams RD, et al. Can we trust the prediction model? Illustrating the importance of external validation by implementing the COVID-19 Vulnerability (C-19) Index across an international network of observational healthcare datasets. JMIR Med Inform 2021.

35 Lane JCE, Weaver J, Kostka K, et al. Risk of depression, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multinational network cohort study. Rheumatology 2021;60:3222–34.

36 Burn E, You SC, Sena AG, et al. Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study. Nat Commun 2020;11:1–11.

37 Areia C, Barreira P, Montanha T, et al. Neuromuscular changes in football players with previous hamstring injury. Clinical Biomechanics 2019;69:115–9.

38 Younis AS, Abdelmonem IM, Mohamed YR, et al. Hydrogel dressings for donor sites of split-thickness skin grafts. Cochrane Database Syst Rev 2020;2020.

39 Davies L, Cook J, Leal J, et al. Comparison of the clinical and cost effectiveness of two management strategies (rehabilitation versus surgical reconstruction) for non-acute anterior cruciate ligament (ACL) injury: study protocol for the ACL SNNAP randomised controlled trial. Trials 2020;21:1–16.

40 Morales DR, Conover MM, You SC, et al. Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis. Lancet Digit Health 2021;3:e98–114.