Danish University Colleges

Report C3 test Lubeck and Kiel Germany

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Test of the medical device
Cortrium – C 3

Department of Radiation Oncology, University Medical Center Schleswig-Holstein
Lübeck, Germany

Department of Radiation Oncology, University Medical Center Schleswig-Holstein
Kiel, Germany

ClinicalTrials.gov Identifier: NCT03387891

Test Design, Process, Results and Recommendations

Slagelse December 2018

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1 Summary

The Cortrium C 3 device, provided by the company Cortrium, was tested at Department of Radiation Oncology, University Medical Center Schleswig-Holstein, Campus Lubeck and Campus Kiel. Department of Radiation Oncology, University Medical Center Schleswig-Holstein ensures treatment and care for patients with cancer. This clinical trial part of the EU Interreg project, InnoCan, which focuses on improving the quality of cancer treatment for patients admitted to Department of Radiation Oncology, University Medical Center Schleswig-Holstein during their cancer treatment.

The purpose of the study was to evaluate measurement properties and feasibility of using a Vital sign Monitoring System for cancer patients under treatment.

Patients at the oncology ward were asked to participate during their admission to hospital. The test, including patients indicated that the C3 device is useable as a healthcare innovation when measuring vital signs.

The advantages for introducing a vital sign measurement to oncological patients is to reduce the constant disturbance of measuring vital signs day and night ensuring the patients rest to recover as well as easing the workflow for the healthcare professionals conducting measurements.

During the test interviews were conducted with healthcare professionals (nurses) as well as patients which could describe their experience of using healthcare devices such as the C 3 during their treatment and care of the patients. Subsequently the interviews with the patients described their experience of using the device.

The initiation visit and start of the test in Lübeck was 04th May 2017 and in Kiel 04th June 2018. The last patients included and finalized the trial in Lübeck was 30th June 2017 and in Kiel 27th September 2018.
The total inclusion of patients was in Lübeck: 15 patients and Kiel: 14 patients.

2 InnoCan and Interreg

This clinical test of the C 3 device is part of the InnoCan project. InnoCan is funded by “Interreg Deutschland-Danmark” with funds from the European Regional Development Fund. The project started in January 2015 and runs for 3 years with a budget of 4.3 million Euro. The project has 10 partners from the region of Zealand, the region of Southern Denmark and the German region Schleswig-Holstein. The partners are hospitals, innovation centres, educational institutions, patient associations and a private company. See for more information on www.innocan.org and www.interreg5a.eu.

This clinical test is one of the four innovative technologies that was tested within the InnoCan project. Experiences from the test will be used for the development of a cross border test centre. The overall goal of the InnoCan project is to preserve and improve the quality of cancer treatment.

A fact that people are living longer means that the ratio of elderly cancer patients will increase. Within the next decade the number of new cancer patients will be increased with
30 percent within the geographic region of Interreg Deutschland-Danmark (south Denmark & northern Germany).

The sub goals in the InnoCan project were:

- Test of 4 innovative technologies in cancer treatment in the region. Companies must be offered easier access to evaluation and testing of their new innovative technologies. The goal is to reduce the time it takes for the new technology to penetrate into the health care sector.

- Development and establishment of a test centre for innovative monitoring technology. The test centre will function cross-border and have employees in both Denmark and Germany. The test centre will be a portal to the health care sector for companies with innovative solutions.

- Development of shorter and more gentle treatment methods with same effect but less side effects for 5 well defined cancer types.

- Creation of a common database for the big cancer types. Data will be updated continuously, and it will be possible to monitor improvements in treatment, including service and patient satisfaction. In depth analysis of register data will support long term improvement of quality of treatment.

2.1 Participating parties

**Manufacturer**
Cortrium
Erik Husfeldt Vej 7
DK-2630 Høje Taastrup
Denmark

**Test sites**
Department of Radiation Oncology, University Medical Center Schleswig-Holstein
Ratzeburger Allee 160
23562 Lübeck,
Germany

Department of Radiation Oncology, University Medical Center Schleswig-Holstein
Arnold-Heller-Straße 3
24105 Kiel, Germany

**Other Parties**
University College Absalon
Slagelsevej 7
DK-4180 Sorø

Design School Kolding (DSKD)
2.3 Role of the participating parties

Cortrium had developed the C3 device. The C3 device contains sensors that monitors Electrocardiogram (ECG), Respiratory rate (breathes per minute), and Body surface temperature. Also, the C3 device contains an accelerometer for registration of the body posture.

The following thesis were aimed to be tested:

Thesis 1) Pulse: The C3 device produces clinically validated pulse data.

Thesis 2) Respiratory rate: The C3 device produces clinically validated respiratory rate data (breaths per minute).

Thesis 3) Infection: With no justified statistic significant correlation between skin and body temperature, the study is exploring how to prevent aggravated or lethal outcomes of cancer treatment, e.g. chemotherapy, by using vital signs measurements combined with accelerometer data to detect infection levels.

Thesis 4) The qualitative study: The study will report the advantages and disadvantages regarding new technological solutions, and the change in workflow and healthcare provision as it is experienced by the healthcare personnel and the patients. The data validation studies (thesis 1-3) were tested in comparison with golden standard measurements methods and/or data validated medical equipment.

Corrtium provided the C 3 devices for this test. Accessories like plastic covers, lpads, cords were provided. Department of Radiation Oncology, University Medical Center Schleswig-Holstein at Campus Lubeck and later at Campus Kiel were chosen as test sites involving the oncology ward on each premises.

A research nurse from the Campus Lucbeck acted the responsible for the in-house testing on the ward. At Campus Kiel a medical doctor was responsible for the test. University College Absalon were responsible for the test as a joint venture with the Innocan local team who were residents at the Campus Lubeck site. The Innocan coordinator overlooked the test site and monitored the progress during the test in Lubeck on daily basis. At Department of Radiation Oncology, University Medical Center Schleswig-Holstein campus Kiel the test was overlooked by one of the Medical Doctors from the Radiation Oncology.

University College Absalon had the responsibility of the actual test as well as the final report. However, Department of Radiation Oncology, University Medical Center Schleswig-Holstein at Campus Lubeck and Campus Kiel played an overall coordinating role concerning the actual testing at the hospital. Researchers from University College Absalon were active players on collecting the test data through observation and interviewing
participating patients and healthcare professionals as well as analysing data afterwards. PFI acted as a work package leader and coordinated communication between the involved partners and the lead partner (Naeststed Hospital). PFI further had a role in the communication between the company Cortrium and the InnoCan project group. The project group intended to incorporate learnings from this clinical test in their evaluation of all the C3 test sites and in the development of future research.

3 Background

In cooperation with Health Innovation Regional Zealand (PFI), Kolding Design School, University College Absalon, Department of Radiation Oncology, University Medical Center Schleswig-Holstein at Campus Lubeck and Campus Kiel wanted to test a medical healthcare device to get an understanding of how to select and implement new healthcare solutions for continuous monitoring of vital measurements. This was done in order to enhance patient safety, experience, treatment, mobility and rehabilitation. This test has been one leg of a series of tests on patients admitted to hospitals in Denmark and Germany under EU’s INTERREG 5a program.

This rapport represents the test at the Department of Radiation Oncology, University Medical Center Schleswig-Holstein at Campus Lubeck and Campus Kiel. The purpose was to test measurement of vital signs with the newly developed wireless monitoring technology, the C3 device developed by the company Cortrium. The purpose was to compare parallel measurements of pulse, respiratory rate and temperature, respectively measured according to current clinical practice at Department of Radiation Oncology, University Medical Center Schleswig-Holstein at Campus Lubeck and Campus Kiel and by the newly developed wireless monitoring technology the C3 device. Similarly, the aim was to get insight into patients’ experience wearing and being monitored by the C3 device, and furthermore how health care professionals experience involvement of the C3 device in the care and treatment practice.
**4 The Medical device**

Healthcare technology is an overall focus in healthcare practice - and particular solutions that are cheap, small and easy to use, and in that perspective can monitor patients in their homes, as well as in the hospital.

The company Cortrium has developed a wearable cost-effective medical device, the C3 device (picture above), for measuring a number of vital signs. The C3 device is placed above the sternum with three standard ECG electrodes attached. The C3 sensors allows the measurement of 3-channel ECG, surface temperature, respiratory rate and accelerometer data. In addition to this, several measurements can be extracted from to the sensors e.g. heart rate, variation in heart rhythm, pace count and body position. The C3 device connects wirelessly via Bluetooth to a phone or a tablet, where the measured parameters can be read. In this project, the C3 device communicated with iPad Mini (Apple).

**4.1 Clinical context**

The C3 device was tested on patients with cancer at an in-house test at Department of Radiation Oncology, University Medical Center Schleswig-Holstein. The Department of Radiation Oncology ensures treatment and care for patients with cancer. The treatment modalities include a wide range of non-surgical oncological modalities focusing on cancer chemotherapy, biologically targeted drugs, and radiotherapy. Department of Radiation Oncology, University Medical Center Schleswig-Holstein complies with international accepted guidelines and standards in Germany.

The patients were included in the project by the clinical research nurse and Professor in charge at Department of Radiation Oncology, University Medical Center Schleswig-Holstein at Campus Lubeck and Campus Kiel.
Research Nurses on duty managed the C3 device during the trial period supervised by the Medical Doctor on duty. In case of technical problems such as corrections with the device itself the manufacturer Cortium supervised and managed potential errors. In the future the C3 device can potentially be used to react if vital signs are changing in patients with cancer, and then treatment can be initiated at a much earlier stage. In addition, the patients do not experience being disturbed all the time during admission to hospital when using the C3 device. Furthermore, the device can ease the workload of nurses in their daily routines. However, it can be a challenge to ensure correct measurements. It must be emphasised that the clinical eye of a nurse working with cancer patients cannot be replaced by a measuring device and the technology measurements must never replace the physical as well as clinical assessment of a patient with cancer.

5. Aim of the test

The aim of the clinical test with the C3 Device was

- To explore the usability of the C3 device when measuring vital signs in patients with cancer admitted to hospital
- To evaluate the paired measurement of the C3 device, by comparing the test results of the vital sign measurements
- To explore the possibilities of enhancing the treatment, care and wellbeing for patients with cancer by interviews with healthcare professionals as well as patients

The C3 test have great potentials for the future care and treatment of cancer patients as the product could improve the quality of life for this patient group by allowing continuous monitoring during hospital admission instead of being monitored manually which creates disturbances both night and day. By introducing a device such as the C3 patients with cancer may experience a more flexible day with less disturbances.

5.1 Why do the company Cortrium want to test the product?

The company Cortrium aimed to investigate if there are potential opportunities for a device like the C3 to measure vital signs whilst admitted to hospital. They want to explore the usability of the C3 device at the hospital as well as understand what the healthcare professionals and the patients think of the device.

5.2 Why are the hospital interested in the test?

Department of Radiation Oncology, University Medical Center Schleswig-Holstein Campus Lubeck and Kiel are investigating new methods to care and treat elderly patients with cancer with the focus on closely increasing quality of life, reducing days of hospital admission as well as innovative solutions in order to shift the healthcare professionals
work in a more effective way. By participating in this test, Department of Radiation Oncology, University Medical Center Schleswig-Holstein Campus Lubeck and Kiel wished to investigate if the C3 device could be used by patients in cancer treatment admitted to hospital. The hospital wished to participate in the test verifying if the C3 device measures precise during use, if the technology worked and how it was received by healthcare professionals as well as patients. Further the project is part of already existing research on oncology and elderly care.

6. Test design

The study was of explorative character. The study consisted of a quantitative cross-sectional study. Paired measurements of vital signs taken with standardized equipment as well as with the C3 device. Furthermore, qualitative interviews and observation studies of the healthcare professionals as well as the patients were conducted.

Prior to the test in Kiel the medical doctors had to conduct a foundation training for investigators conducting a clinical trial according to the Medical Device Act (Germany), otherwise they were not allowed to conduct a clinical trial with medical devices according the German regulations.

The recruitment was conducted from newly admitted patients at both Lubeck and Kiel Oncology departments. In total 27 patients were included in the project. Five patients in Lubeck and 3 patients in Kiel were interviewed about their experience of being introduced and using the C3 device. Ten C3 devices and three iPad Minis were included in Lubeck and two Ipads in Kiel. The devices were after being cleaned and charged used again.

6.1 Inclusion criteria:
Able persons, >18 years of age with a cancer diagnosis and in treatment at the oncological Department. German speaking patients.

6.2 Exclusion criteria:
Pregnant or lactating women and fertile women who were not using contraception. Not legally competent patients, Patients under 18 years. Patients with known heart-related disease

6.3 Informed consent:
The clinical research nurse in cooperation with the Professor in charge was responsible for the recruitment. Participants were given the oral and written information about the project by a medical doctor. Dependent of the medical condition of the patient the information was given right after admission to Department of Radiation Oncology, University Medical Center Schleswig-Holstein.

In case the admission happened during evening and night shifts the oral and written information were given the next day. Apart from the written patient information describing the test purpose the patient was given sufficient time to consider participation before given the informed consent. As the test consisted measurement of vital signs during the acute
phase of admission consent of participation was important. The patients were informed that participation in the project was voluntary, and that they could withdraw from the project at any time without any consequences for their further treatment.

7. Ethical considerations

Ethical considerations were kept both at the test of the C3 at Campus Lubeck and Campus Kiel. No biological material was gathered as part of the clinical trial and thus no authorization was needed both including patient data as well as data from the interviews with patients and healthcare professionals.

In the test of the C3 device on the ward the clinical test was conducted without Internet access. Data was stored on the C3 device and the individual iPads. Data transmission from the C3 device to iPads was encrypted. The clinical trials are conducted in compliance with the Guidelines for "Good Clinical Practice" DS / EN ISO 14155: 2011", and the collected scientific data was handled in accordance with the Law concerning the processing of personal data.

Qualitative interviews were conducted with patients as well as with healthcare professionals. The interviews were digital recorded and transcribed verbatim. The recordings were stored and handled on a secure server at University Absalon. Only the researchers involved in the test had access to the data as required by the EU Data Protection Regulation (GDPR). Digital recorded interviews and transcripts were destroyed 30 days after completion of the test.

The patients participating in the C3 test received written information about the test. The patients were offered an additional interview about participation in the test and that they had time to consider their participation before signing up for the test. Consent were given by the patient themselves.

The participant information and the template patient consent form were forwarded the patient and each patient were asked to sign a document (proxy statement) that allowed the Medicines Agency and the relevant foreign health authorities’ access to the patient records for inspection and control of the test. Included patients in the test could at any time during the trial testing period withdraw his or her inclusion - without facing a deterioration of their planned treatment.

The patient data from the C3 device was analyzed only in connection with the clinical test. The data was not subject to any clinical decisions made during the patient’s admission to hospital or causing delay in the treatment of the patient. During the cause of the study the C 3 device device received the CE marked for the hearth rate monitoring. Clinical test did not bring influence any planned patient treatment.
8. Test perspectives

Several perspectives were included in the test. First and foremost the company Cortium was interested in the functionality of their C3 device. Would the device be usable in a clinical setting? And most important, were the measurements accurate?

As previously mentioned the user perspective was of great importance. Did implementation of a healthcare device measuring vital signs improve the experience and life quality of patients admitted with fever? Furthermore, the nursing perspective was explored. Would implementation have any impact on the nurses’ workload?

Subsequently it was important to explore the ethical considerations and the patients’ autonomy when implementing a new technological device. When implementing new tests on patients with cancer some resistance to participation is expected from the patients, the healthcare professionals as well as from the relatives.

Economy is a continuous subject in healthcare and this project could elaborate of the economical perspectives of introducing online monitoring of patients at the Department of Oncology. Finally, the test and the planned framework can give an insight into the interaction between technology and organization of the medical practice.

9. Test process

The protocol for the test was conducted by Department of Radiation Oncology, University Medical Center Schleswig-Holstein, University College Absalon, The Design School Kolding, Region Zealand and the company Cortium. The protocol was accepted for research in May 2015. The first patient was included in the project February 2016 and the inclusion of patients ended ultimo August 2016.

10. Test implementation

After the initial acceptance of the protocol the test design was developed in cooperation between the partners involved in the project. The project was further approved by the health authorities and regional Scientific Ethical Committee.

Observational studies were conducted by The Design School Kolding and University College Absalon prior to the test start and during the test.

Prior to the implementation of the patients the clinical research nurse ensured that the physical location was prepared for the tests. This included storing of the devices, loading of devices and iPads. Ensuring the hygienic regulations were enforced. The manual with guidelines for using the device were updated.
Furthermore, the healthcare professionals were informed and instructed about their roles in the test.

The data from the C3 device were collected on an iPad Mini. At the same time data from a manual collection of vital signs were collected by the nurses at Department of Radiation Oncology, University Medical Center Schleswig-Holstein.

The 7 patients who were involved in the project were interviewed by a researcher from Absalon University College. Additional observational studies were conducted.

Interviews with a total of 5 nurses and two medical doctors working at Department of Radiation Oncology, University Medical Center Schleswig-Holstein were conducted by researchers from University College Absalon. Qualitative and quantitative data analysis were conducted by researchers from University College Absalon.

11. Procedure

The framework of the initially planned test was followed and the recommendations and best practice from the C3 test at Naestved Oncology Department in Denmark was taken into consideration in order to avoid delay. The test at Department of Radiation Oncology, University Medical Center Schleswig-Holstein at campus Lubeck and Kiel was conducted outside the public holidays. Including patients who were in treatment for cancer implied that careful inclusion and exclusion was followed. However, working with human beings in hospital include sensitive planning.

At Campus Lubeck participating nurses were selected by the Management and they decided when the nurses’ were free to be interviewed. Due to this the period was extended according to the original plan. At Campus Kiel there were no nurses participating in the test as all management with the device was conducted by medical doctors.

According to German regulations the DIMDI platform were causing delay and ethical approval was dependent of this. This caused that the data entrance could not be accessed.

12. Methodology

Different qualitative and quantitative methods have been applied during this test.

Qualitative methods to collect and analyse data
- Observation. Location were observed by trained researchers to gather data on how the test site were suitable.
- Semi structured interviews. Patients were interviewed by trained researchers about
their experience with the C3 device and implementation of health care technology as part of their care and treatment.

- Semi structured interview. Health care professionals were interviewed individually about their view on the use of new technologies in the care of oncology patients.

Data from the interviews were analysed using a thematic analysis approach. Thematic analysis is the process of identifying patterns and themes within qualitative data.

13. Test results

In the following section the test results and the data collected from the interviews with healthcare professionals and patients will be presented in the following order, quantitative results followed by qualitative results.

13.1 Quantitative methods

In order to compare the data in a larger scale the data from both Lübeck and Kiel were pooled in to one data set. In table, one there is an overview of the data

<table>
<thead>
<tr>
<th></th>
<th>Kiel</th>
<th>Lübeck</th>
<th>Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Measurements</td>
<td>102</td>
<td>102</td>
<td>204</td>
</tr>
<tr>
<td>Male/Female (%)</td>
<td>6/7  (46/54)</td>
<td>11/5 (69/31)</td>
<td>17/12 (59/41)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>61,2 (9,5)</td>
<td>64,3 (9,3)</td>
<td>62,7 (9,4)</td>
</tr>
<tr>
<td>Wright, kg (SD)</td>
<td>67,5 (17,5)</td>
<td>72,3 (13,5)</td>
<td>69,8 (15,9)</td>
</tr>
<tr>
<td>Height, m (SD)</td>
<td>1,7 (0,1)</td>
<td>1,7 (0,1)</td>
<td>1,72 (0,1)</td>
</tr>
</tbody>
</table>

Table 1: Characteristic of data from Germany (pooled) Kiel and Lübeck

In order to compare the measurements between the C3 unit and the standard type of measurements a Student’s T-test were performed on the data. The results from these showed a significant difference between temperature and respiration (p<0,001) but no difference for pulse (p>0,05).

<table>
<thead>
<tr>
<th></th>
<th>Standard form of measurement</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration (SD)</td>
<td>14,2 (3,9)</td>
<td>10,6 (7,9)</td>
</tr>
<tr>
<td>Pulse (SD)</td>
<td>74 (12,8)</td>
<td>76,3 (17,9)</td>
</tr>
<tr>
<td>Temperature (SD)</td>
<td>36,6 (0,56)</td>
<td>35,9 (1)</td>
</tr>
</tbody>
</table>

Table 2 Mean (± SD) for all measured vital values
In the Bland Altman plots (fig 1-3), the differences between the C3 and standard measurements are illustrated. The two dotted lines represents upper and lower limits of agreement (mean±1,96*SD).

**Figure 1:** The Bland Altman Plot shows the C3 has a negative tendency at low repertory rates and positive at high repertory rates. Mean difference: -4.1, Upper Limits of agreement: 8.1, Lower limits of agreement: -16.3.

**Figure 2:** The Bland Altman Plot shows the C3 has a negative tendency at low repertory rates and positive at high repertory rates. Although the difference is less pronounce than respiration and temperature. Mean difference: 1.9, Upper Limits of agreement: 23.9, Lower limits of agreement: -20.1.
In order to investigate whether measurements from the standard and the C3 device were correlated, a regression analysis was performed. A correlation was found only for pulse (p <0.001).

13.2 Quantitative results (summary by University College Absalom)

In conclusion, the statistical tests indicate that the two methods of testing, the standard and the C3 device, did not measure the same for respiration and temperature. When pulses were measured, there was no difference. The correlation analysis showed a correlation between the measurements from the C3 device and the standard for pulse, but for respiration and temperature, there were no correlations.

16.3 Qualitative research

One of the important deliverables in the C3 test was the user perspective, which is presented as the Patient perspective as well as the perspective from the healthcare professionals (nurses and doctors) involved in the test.

In the following excerpts of the experiences by the patients and nurses are presented. The experiences are presented under the following themes.
16.3.1 The patient perspective:

Generally, the patients who participated in the project expressed that they were well informed, and they did not feel uneasy about participating. Most of the patients did not experience any discomfort wearing the device. One patient took it off after some time. They did not notice the device once it was on as only in brief mentioned the light as being bright. One patient suggested the tape fastening the device was not very strong. A female patient felt due to her large breasts that the device got caught on her chest. Most patients saw an advantage of using the device 24 hours a day during hospital stay. They did not get disturbed by nurses measuring vital signs and they could move away from the hospital bed wearing it. Though there was positive feed-back the patients were mentioning that they were worried about sending the data from device to Ipad. Would the data be safe and the measurements registered accordingly. The patients did worry that by using the device they did not see and speak with the nurse as much as before and they did not like this perspective. However, they all saw implementation of healthcare technology as positive particularly during cancer treatment where measuring and detecting vital signs are important for the treatment and care. Further they could envisage a monitoring device such as the C3 being used when the patients are in their own homes.

16.3.2 The Nurses perspective in Lubeck:

After the interviews with the nurses it can be concluded that the overall reaction to the test of the C3 device was positive. They found the instructions and the manuals were readable and the charging and storing could be done. The introduction to the test went well. During the test there were errors in the connection between the C3 device and the Ipad. This caused concern and was time consuming for the nurses. It was mentioned that handling healthcare technology was a “man” thing and that using innovative solutions could make more male nurses interested.

Storing the device and keeping the hygenic regulations was another concern. The C3 device could contain germs as it was difficult to clean in depth.

The nurses in Lubeck were raising concern about the face to face contact with the patients. Would the device mean that they did not go into the patients room as often as they would measuring manually. They argued that not every observation could be done by technology – such as the patient being sad, concerned, needing a hand to hold or just wanting to chat.

13.3.3 The doctor´s perspective in Kiel:

The doctors interviewed mentioned that as the C3 device was new in the department it was more time consuming using it than it benefitted the patients as well as healthcare professionals. They emphasise that it is noticeable that the c3 device is not fully developed yet. Further they argue that it is difficult to discuss as they as doctors do not measure the vital signs as it is the nurses who care for that.
14. Economy

No economical compensation was given in the project to either healthcare professionals or patients participating in the project. The completion of the project was conducted by the nurses and doctors at Department of Radiation Oncology, University Medical Center Schleswig-Holstein Campus Lübeck and Campus Kiel. The C3 devices as well as the iPad Minis used in the project were sponsored from external sources. The Oncology Department had sponsored 3 iPad Minis themselves. Subsequently implementing healthcare technology in general may have an economical benefit such as monitoring the patients at home during treatment and care. However, in this test of the C3 device the focus has not been on the economic benefit but on assessing the use of the device for patients submitted to oncology treatment and care. Further the experience of nurses caring for as well as monitoring the patients whilst using the device has been the focus. More research is needed with focus on the economic benefit in this area.

15. How does Innovative solutions such as the C3 device fit into the treatment and care of cancer patients in oncology

Resistance to new technology and resistance to change is a potential threat from employees, healthcare professionals, patients and relatives. However, this test has proven that there is an opening in implementation technology into the treatment and care of patients with cancer and potentially others. Although the quantitative data indicated an error in measuring the vital signs using the C3 device -the error was consistent and an adjustment of the C3 device is necessary and required in order to be implemented as a healthcare technology tool when measuring vital signs in patients generally.

16. Challenges the in the project

There were 10 challenges had to face during the C3 tests in Lübeck and Kiel

1) **Translation of and changes in the trial protocol.** The original trial protocol was written in Danish a translation into the English language was required. There was a different understanding between the Danish and the German participants if the trial protocol has to be translated in full or only partly, which took quite some time. The inclusion and exclusion criteria had to be modified due to different patient populations.

2) **Clarification of data protection rules for trials in the hospital.** Meeting with the data protection representative and completion of several forms.
3) **Preparation of contracts with Cortrium** (Clinical Site Agreement, Data Treatment Agreement)

4) **Support of Cortrium in order to prepare for the medical device trials in Germany**, e.g. by
   - informing about the regulatory requirements
   - adapting/translating some of the documents required for the German market
   - explaining the setup of the ethics committee, the Federal Institute for Drugs and Medical Devices (BfArM), supreme state authority (Landesamt für Soziale Dienste Schleswig-Holstein), DIMDI

5) **Coping with the differences of medical research between Denmark and Germany.** E.g. different responsibilities of nurses with regard to research and different requirements for documentation and monitoring of clinical trials. Conducting monitoring is mandatory in Germany as well as the preparation of a Trial Master File, Investigators Site Files and a Monitoring Manual.

6) **Only the company had access to the DIMDI database and had language difficulties when submitting the application to the authorities.** E.g. “Absehen von der Genehmigungspflicht” - The BfArM can waive the authorization in case of clinical trials of medical devices with a low safety risk. By mistake the full application was requested when pushing the wrong button on the DIMDI platform. This led to some additional work and additional costs. The test center took over the submission of the application.

7) **Uncertainties with regard to the supplies of the device**, i.e. the right electrodes had to be found, some did not stay attached to the skin for a longer duration (24h)

8) **Supreme State Authority conducted inspection of the test in Lübeck (June 2017).** Required adaption of trial documents and amended submission to DIMDI.

9) **Extension of insurance** due to longer duration of the trial. Required adaption of trial documents and amended submission to DIMDI.

10) **Data security and data protection requirements** had to be adapted at the beginning and at the 25th of May 2018. Required adaption of trial documents and amended submission to DIMDI.
17. Summing up on the process

The C3 test at Department of Radiation Oncology, University Medical Center Schleswig-Holstein Campus Lubeck and Kiel was the second and third test of a prototype testing of the device. Introducing the device proved obstacles, however only to be expected when testing a new medical solution on patients who are hospitalized. The test needed two steps. Step one, that the nurses are trained in using the device and familiarize themselves in the technology, the manual and the communication with the patient. The step two, recruiting patients suitable to be included in the test. Recruiting patients for the test turned out to be very easy. Patients were very willing to participate. Testing on patients admitted to hospital showed that it is necessary to have nurses and doctors from the hospital to take an active role in the test. In future tests, awareness of time and resources would be recommended. Further acknowledging that nurses have different approaches to working with health care technology. Interviews with nurses and patients participating the test were conducted in order to get the nurse and patient perspective working with and around the C3 device.

The results from the C3 test at Campus Lubeck and Campus Kiel have been presented separately and pooled together. Subsequently the joined results indicate that a device like the C3 is useable when caring and treating patients with cancer during their hospital admission. The results from the device prove that implementing an innovative device such as the C3 when measuring vital signs is reliable and give the patients a better quality of life during admission to hospital. The healthcare professionals have a healthy approach to implementing the device and generally suggest that innovative healthcare solutions can be used in their daily care and treatment of the patients. Concerns were mentioned such as accuracy, hygiene, errors and time. Further studies about the use and functionality of the device could be done in order to answer some of these questions.

The paired measurements from the C3 devices as well as manual data taken by the nurses were analysed and produced a data set which indicated that the measurements were reliable and stable.

18. Recommendations to the hospital

As the use of healthcare technology increasingly are being introduced to the hospitals recommendations as well as best practice is needed.

The pilot test of the C3 device was tested on a very few patients as well as the follow up interviews made with both nurses and patients.

It is indicated that using the C3 device monitoring vital signs in patients with cancer generally has been successful. In order to facilitate the best care and treatment for the patients during their cancer treatment recommendations has been made to the manufacturer. An example could be the C3 device being too bright during the night when the patients are trying to sleep.
Another recommendation is the size of the C3 device as it needs to fit on the chest of the patient without the patient feeling uncomfortable.

Storing the C3 device and the IPads Mini in a convenient and safe place on the ward where there is space for as well as access to charging is important. Further attention to continuous cleaning of all the devices used is important in order to follow the hygienic regulation of the hospital.

Implementation of healthcare technology is generally new for nurses. In this test the nurses were interviewed about the pro and cons of using the C3 device caring and treating patients with cancer.

A thorough introduction of the nurses to the background and the use of the device is vital when implementing new healthcare technology. The manual for the nurses is recommended to be easily read and understood. In case of errors on the devices help must be easily accessible on the ward.

19. Recommendations to the Manufacturer

The design of the C3 device proved to work well for patients in bed as well as patients standing up. Only one patient experienced that the device got loose and needed to be refitted. Charging the device did not seem to have any problems. Issues about hygiene should be investigated further. There were incidents where the light on the C3 device was disturbing and this issue has been forwarded to the manufacturer.

Further during the test there was situations where plastic covers for the device ad Ipad were not fitting which disturbed the test.

All immediate errors and incidents with the C3 device were reported to the manufacturer in order to correct or replace so the test was not delayed unnecessary.

Feedback was reported back to the manufacturer as adjustments were needed during the test or other problems needing immediate attention occurred. An example could be hygienic regulation problems due to crack in the surface material of the C3 device. Or patients noticing the lights on the device disturbing them sleeping.

Recommendations were sent to the manufacturer Cortrium at the end of the test in enabling the manufacturer to make adjustment. These recommendations are being held confidential due to the agreement between the manufacturer and Innocan.
Appendix – study protocol
Authors
Christina Louise Lindhardt, PhD, MSc, RN, Project Manager University College Absalon

Thank you to:
Mette Gajlhede, Lektor, MSc University College Absalon for the statistical documentation

Published papers

InnoCan has the following partners

Partners are responsible solely for their own statements and presented results in the project.
Appendices

Protocol

Clinical testing on newly developed monitoring technology (The Cortrium C3 device) for continuous measurements of ECG, respiratory rate, body surface temperature and accelerometer data for patients with cancer.

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1.1. 1. The Sponsor

1.1. The sponsoring company.
The responsible sponsor is the Danish registered company; Cortrium (Company business number: DK36445335). The Sponsor is hereinafter mentioned as Cortrium.

Cortrium contact data:
c/o Rocket Labs, Hejrevej 30, 1.
DK-2400 Copenhagen NV
Tlf. +45 40574771
e-mail: info@cortrium.com

1.2. Authorized person at Cortrium
The authorized person at Cortrium for signing the protocol, documents and any amendments is Jacob Eric Nielsen (COO).

1.3. Medical doctor advisor
There is no external medical doctor advisor associated with the clinical trial testing.

1.2. 2. Participating clinical test sites (Investigators)
Two clinical test sites at University Medical Center Schleswig-Holstein (UKSH) are testing the Cortrium C3 device, cf. 1) Department of Oncology and Hematology, Campus Lübeck, and 2) Department of Radiation Oncology, Campus Kiel.

2.1. Campus Lübeck (1. Investigator)
At Campus Lübeck, the clinical trial testing is located at the Department of Oncology and Hematology, Ratzeburger Allee 160, 40, D-23538 Lübeck. The department contact details are: e-mail: strahlentherapie-hl@uk-sh.de, and Web: http://www.onco-kiel.uk-sh.de/Strahlentherapie+._+Campus+L%C3%BCbeck-p-22.html. The authorized person at Campus Lübeck for signing all documents including the protocol with any amendments is Prof. Dr. med. Dirk Rades (Head of Department), e-mail dirk.rades@uksh.de, Phone +49-451 500 45400.

Cortrium and Campus Lübeck have signed a clinical site agreement (Exhibit 1a).

2.2. Campus Kiel (2. Investigator)
At Campus Kiel, the clinical trial testing is located at the Department of Radiology, Arnold-Heller-Strasse 3, 23, D-24105 Kiel. The department contact details are silke.eckert@uksh.de, and Web:
The authorized person at Campus Lübeck for signing all documents including the protocol with any amendments is Prof. Dr. med. Jürgen Dunst (Director of the Departments Kiel/Lübeck), e-mail: juergen.dunst@uksh.de, phone +49-431 500 26500. Cortrium and Campus Kiel have signed a clinical site agreement (Exhibit 1b).

2.3. Other participating parties

There are two participating parties connected to the clinical trials as educational and research institutes regarding nurse studies of work flow and patient empowerment when introducing new wearable tech monitoring solution.

1) University College Sjælland (UCSJ): UCSJ is participation in their capacity as nursing educational school and research centre. The contact details are: Ass. Prof. Lene Bjerregaard, Center for Nursing and Bioanalytics, Ingemannsvej 17, DK-4200 Slagelse, phone +45 72482173, e-mail: lebj@ucsj.dk.

2) The Design School Kolding (DSKD): DSKD is participating in their capacity as an educational school for welfare technology design of communication between healthcare professionals and patients. The contact details are: Ingrid van Rijn (MSc), The Design School Kolding, Ágade 10, DK-6000 Kolding, phone +45 50103399, e-mail: ias@dskd.dk.

1.3. 3. Time schedule

3.1. Clinical trial start-up

The clinical trial testing is starting immediately after the approval from Bundesinstitute für Arzneimittel und Medizinprodukte (BfArD) at Campus Lübeck. Clinical trials start up at Campus Kiel will be postponed to four weeks after the start at Campus Lübeck. To avoid any doubts about the thesis under testing, Cortrium will report the online platform http://www.clinicaltrials.gov about the thesis under testing before startup. The EU platform for registration of clinical trials; http://www.clinicaltrialsregister.eu, is not yet open for a test of medical equipment.

3.2. Time schedule at Campus Lübeck and Campus Kiel

The duration of the clinical trial testing of the C3 device follows the same schedule though the trial at Campus Kiel is delayed in start-up by four weeks. All together the testing period of the C3 devices is estimated to be 13 weeks - or until approximately 20 patients at each campus have been testing the Cortrium C3 device. The total duration process of the trials including data analysis and article writing is expected a duration of 26 weeks. At the submission date of the protocol to BfArD, no specific scientific journals are chosen for publishing the trial test results.

Table 1: Clinical trial testing at Campus Lübeck and Campus Kiel (overview)

<table>
<thead>
<tr>
<th>Clinical trial testing C3 device</th>
<th>1. week</th>
<th>2. week</th>
<th>3. week</th>
<th>4-10. weeks</th>
<th>11. week</th>
<th>12. week</th>
<th>13-26. week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting the clinical trial testing: Clinicaltrials.gov</td>
<td></td>
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<tr>
<td>Start-up: Kick-off meeting - Delivery of C3 devices and manuals</td>
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<td></td>
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<tr>
<td>Patients: Recruitment (Dialogue patient - nurse)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20 patient: Monitoring patients with C3 device</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20 patient: Monitoring patients with medical CE-marked equipment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weekly status updates/meetings between stakeholders</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hygiene: Preparation/cleaning of C3 devices</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Interview: Patients (6 interviews)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Interviews: Nurses and other healthcare personnel (5 interviews)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events: Reporting to BfArD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical analysis (Bland-Altman plots) &amp; Qualitative analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publishing: Writing of article(s) (clinical data validation/interviews/observational studies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsible parties</td>
<td>Cortrium</td>
<td>Campus Lübeck</td>
<td>University College Zealand (UCSJ) &amp; Design School Kolding (DSKD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As outlined in Table 1, the involved parties in the clinical trial testing will hold weekly status updates meeting. It is expected that the majority of these meetings are held as conference call
meetings. The agenda for each status meeting is 1) update on a number of patients having finished the trial testing 2) including remarks about the performance of the C3 device. The trial testing is part of the InnoCan project financed by the EU funding scheme; Interreg 5A programme. All parties involved in the clinical trial testing of the C3 device are partners in InnoCan.

4. Why testing the Cortrium C3 device?
The development of new and inexpensive wireless technology sensors affixed to the body (wearable-tech) that transfer the measured data to mobile devices and cloud service solutions have great potential for monitoring and diagnosing patients. Continuously monitoring of patients' health data at the hospital or in the home of the patient are pathing the way for very early detection of critical developments in the patients' health data (Vital parameters). The Cortrium C3 device represents such a novel technology sensor. But research in these novel sensor technologies is scarce with included patients in hospital settings. There is no clear evidence that the measured data is of diagnostic quality, and whether wearables-tech is a progressive step forward in the busy and stressful daily routines of the healthcare professionals.
The purpose of the clinical trial testing of the Cortrium C3 device is to contribute to the clinical research in Germany and Denmark. As Cortrium has developed a sensor (The C3 device) that streams data measured health data to a mobile device (iPad), and further to cloud-based servers, that enable the users (healthcare personnel and patients) access to all data in remote (website). The Cortrium browser-based cloud services are not part of the clinical trial testing at UKSH. Instead, the clinical trial testing is exclusively focusing on data validation of the measured vital sign parameters from the C3 device.
But the clinical trials at UKSH are brought into the perspective of a qualitative study of the future usage of wearables-tech at hospitals. The qualitative study will be based upon observational studies and interviews with the patients and healthcare personnel participating in the trials. As very few studies have been carried out in the field of wearables-tech at hospitals, the parties expect international attention. Some the already conducted trials in wearables-tech are analyzed in the Cortrium; "Investigators Brochure".

5. The C3 device - Introduction to the equipment
Cortrium has developed the C3 device. The C3 device contains sensors that monitor the following parameters: 1) Electrocardiogram (ECG), 2) Respiratory rate (breathes per minute), and 3) Body surface temperature. Also, the C3 device contains an accelerometer for registration of the body posture. The C3 device does not hold the medical CE-marking. 

**Photo 1:** Photo 1 (left) shows the C3 device including three standard ECG electrodes. 
**Photo 2:** Photo 2 (right) shows the C3 device separated cf. the PCB print and the plastic shielding cans.

The weight of the C3 device is 25 grammes. The C3 device contains a 3,7' rechargeable Li-on battery. Recharge via the standard microUSB port on the side of the C3 device. A fully charged battery guarantees at least 24 hours recording time of sensor data, which is equivalent to recommended usage time of the ECG electrodes for long time monitoring.

5.1. The C3 device - manual
The C3 device is automatically activated when adhered to the torso of the patient. There is no turn
off the bottom on the C3 device. Before the device is adhered via the ECG electrodes, the healthcare personnel start the device by light touching the lifted plastic part. Hereinafter the C3 device is located with the adhering electrodes on the torso of the patient at a distance of no less than 10 cm from the heart. The C3 device has three minutes to recognize a programmed recognizable ECG signal. When the ECG signal is identified, the C3 device will start the recordings of the vital sign parameters as long as the battery is charged, and at least one ECG electrode adheres the torso. All recorded data is stored on an embedded memory card within the C3 device.

A short illustrative guiding manual of starting and ending a recording is produced for the healthcare personnel by Cortrium. The manual is enclosed as Exhibit 2 to the protocol. The usage of the C3 device does not require any instruction or training once the manual is in the hands of the healthcare personnel. There are no medicine procedures prior to the usage of the C3 device. Cortrium offers full service throughout the trials of any questions related to the use of the C3 device by the healthcare personnel or the patients.

### 5.2. The C3 device - LED light indicators

The Light Emitting Diode (LED) on the Cortrium C3 device can display colours in different mode flashes. Each colour and mode flash indicates various conditions of the C3 device:

**Table 2: C3 device colour display and mode flashes (overview)**

<table>
<thead>
<tr>
<th>Color display</th>
<th>Flashing modes of each colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>GREEN - Associated with recording</td>
<td>• Constant on</td>
</tr>
<tr>
<td>BLUE - Associated with the Bluetooth connection</td>
<td>• Flash slow (0.5 seconds on - 0.5 seconds off)</td>
</tr>
<tr>
<td>RED - Associated with the battery status</td>
<td>• Flash fast (0.1 seconds on - 0.1 seconds off)</td>
</tr>
<tr>
<td></td>
<td>• Blip (ultra-fast and subtle flash of 0.004 seconds)</td>
</tr>
</tbody>
</table>

**Recordings - Indications**

<table>
<thead>
<tr>
<th>GREEN flash slowly for 30 seconds</th>
<th>The device has detected a stable connection between body and electrodes and recording has been successfully initiated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GREEN blip</td>
<td>The device is recording.</td>
</tr>
<tr>
<td>GREEN &amp; BLUE blips</td>
<td>When recording while connected to the app, the GREEN and BLUE blips will indicate that everything is working properly. When recording without connection to the app, only the GREEN blips we be seen.</td>
</tr>
</tbody>
</table>

**Bluetooth - Indications**

<table>
<thead>
<tr>
<th>BLUE flash fast</th>
<th>Bluetooth advertising. The device is ready to connect to the iOS app. Flashing stops and blips start once the connection is established. This mode is initiated by tapping or shaking the C3 device.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLUE blip</td>
<td>The device is transmitting via Bluetooth.</td>
</tr>
</tbody>
</table>

**Lead-off detection and battery indication**

<p>| RED constant on and GREEN flash fast               | Lead off detected. Indicates one or more of the electrodes has lost the connection to the                          |</p>
<table>
<thead>
<tr>
<th>RED flash slowly</th>
<th>Battery level below 10%.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED flash fast</td>
<td>Battery level below 5%.</td>
</tr>
<tr>
<td><strong>C3 device is connected to USB</strong></td>
<td></td>
</tr>
<tr>
<td>RED constant on</td>
<td>The C3 device is charging.</td>
</tr>
<tr>
<td>GREEN constant on</td>
<td>The C3 device fully charged.</td>
</tr>
</tbody>
</table>

**5.3. Connecting the C3 device to the Cortrium app**

The healthcare personnel can at any time connect the C3 device to the Cortrium app on any iOS Bluetooth 4.0 enabled technology (iPod, iPhone, iPad), and obtain a live view of all recorded data.² The Cortrium app is activated like any other app on a smart device or tablet by a light touch on the app icon. When the app is active, the app user must press the touch screen "connect" bottom to establish the Bluetooth connection between the app and the C3 device (see Photo 3). The streaming of data is encrypted to avoid any successful attempt by 3. parties to hack the data.

**Photo 3: Cortrium App screen dump**

When the Bluetooth connection is active, all data recorded on the embedded memory card on the device is also recorded within the Cortrium app. It is also possible to open data streaming to the cloud and review data in remote, though, as already mentioned, the live view is not subject to testing and therefore disabled in clinical trial testing.

The Cortrium app and the use of an iPad in the clinical trials at UKSH are not considered at medical equipment but as accessories to the monitoring device (The C3 device). As the C3 device is recording data independently from the activation of the Cortrium app, the clinical trial testing could be completed without the Cortrium app. But as the clinical trial testing is also subject to nursing research and patient empowerment studies about introducing wearables-tech in hospitals, the accessories to the C3 device is included in the testing.

**5.4. The C3 device and similar equipment on the market**

The C3 device represents a radical change to current existing monitoring medical equipment. The C3 device is working wireless without any cables either to the sensor electrodes or external monitors for data collection. All data is recorded on the embedded memory card, and all data can be streamed to other equipment or servers via the RESTful API data format as long as the receiving equipment is able to receive data in open formats.

**Similar equipment on the market:** Cortrium does not about marketed equipment similar to the C3 device containing measurements of ECG, respiratory rate, body surface temperature, and posture in one unit. Equipment with fewer sensors exists on the market. Most known is the portable Holter ECG monitor. The portable Holter monitor must be carried in a bag hanging around the patients'

² iOS operating systems (version 6.0 and onwards). iPhones: 4S, 5, 5C, SE, 5S, 6, 6 plus, 6S, 6S plus, 7, 7 plus; iPad: 3 & Air; iPadmini: 2, 3, Air; and iPod: 4, 5, 6.
neck and with cables to sensor at least five electrodes on the torso. All data is stored on the Holter in proprietary data formats, and diagnosing is done by using paper print-outs or via a vendor-locked monitor.

Wireless monitoring wearables on the market do not use standard ECG electrodes, but a customized patch ensures the connection to the recording of the biometric data signals. Customized patches reduce the cohort of patient adaptable for being monitored in the event of allergic skin reaction, sweaty or sensitive skin. As standard ECG electrodes are in all shapes and forms, it is almost always possible to identify standard electrodes suitable for the individual patient. No the knowledge of Cortrium, no customized patch-based monitoring device offers an app solution for continuously live streaming of recorded data.

5.5. The C3 device - Body contact

The C3 device does not contain any pharmaceutical drugs or biological material. No carcinogenic, mutagenic or toxic substances are included in the C3 device. All materials are selected for the use of non-toxic substances. Component and manufacturers documentation are checked and kept in the Cortrium quality management system. The components and manufacturing materials are further evaluated in "Investigators Brochure".

<table>
<thead>
<tr>
<th>Table 3: C3 device and body contact - schematic overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The C3 device</strong></td>
</tr>
<tr>
<td><strong>ECG electrodes</strong></td>
</tr>
<tr>
<td><strong>iPhone &amp; iPad</strong></td>
</tr>
</tbody>
</table>

6. The C3 devices in the clinical trials
6.1. Identification of the C3 devices

All delivered C3 devices are new devices not used on any patients or persons before. The functionality of the devices is tested and cleared by Cortrium before delivery. The C3 devices delivered are including software on the device. Further technical specifications about the hardware and software are specified in the "Investigators Brochure".

<table>
<thead>
<tr>
<th>Table 4: The C3 device - Schematic overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hardware</strong></td>
</tr>
<tr>
<td><strong>Form</strong></td>
</tr>
<tr>
<td><strong>Embedded software on device</strong></td>
</tr>
<tr>
<td><strong>Application</strong></td>
</tr>
<tr>
<td><strong>Application software</strong></td>
</tr>
</tbody>
</table>

6.2. Equipment inventory

All the C3 devices delivered for clinical trial testing have unique identification numbers. Solely the C3 devices listed in the table 5 below will be used in the clinical trials.

<table>
<thead>
<tr>
<th>Table 5: Equipment Inventory</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 device - Identification number</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>1. C3 UKSH1</td>
</tr>
<tr>
<td>2. C3 UKSH2</td>
</tr>
<tr>
<td>3. C3 UKSH3</td>
</tr>
<tr>
<td>4. C3 UKSH4</td>
</tr>
<tr>
<td>5. C3 UKSH5</td>
</tr>
<tr>
<td>6. C3 UKSH6</td>
</tr>
<tr>
<td>7. C3 UKSH7</td>
</tr>
<tr>
<td>8. C3 UKSH8</td>
</tr>
<tr>
<td>9. C3 UKSH9</td>
</tr>
<tr>
<td>10. C3 UKSH10</td>
</tr>
<tr>
<td>11. C3 UKSH11</td>
</tr>
<tr>
<td>12. C3 UKSH12</td>
</tr>
</tbody>
</table>

Besides the identification number, all devices have the text imprinted "Cortrium" and "Only for clinical testing", cf. The Medical Device Directive (93/42/EEC). To this extent, Cortrium is in compliance with the ISO standard “Symbols for Use in the Labeling of Medical Devices. (EN ISO 15223-1:2012). Cortrium is retaining a copy of the embedded software on the included C3 devices in the clinical trial. The healthcare personnel will list the identification number of the devices used by the patients included. The listing is shown in the Case Report Form.

The C3 devices can be used on more than one patient. After the patient has been monitored, the C3 device is disassembled and made ready for usage on a new patient. Before used again, the C3 device is cleaned (disinfection) and the battery is fully recharged. The responsible nurses at the hospitals are responsible for the disinfection procedures. In the event one or more C3 devices are defect or malfunctioning, the devices are returned to Cortrium for repair. If Cortrium is unable to repair the device, the device is excluded from the list of available devices.

Cortrium confirms that the devices delivered are in line with all essential requirements; cf. The Medical Device Directive (93/42/EEC) - except all aspects that are part of the clinical trial testing. Regarding the aspects that are part of the clinical trial testing, Cortrium has taken all needed steps to fulfil necessary precautions to protect the patients' health and security (see Exhibit 4).

7. The clinical trials

The clinical trial testing at the C3 device is divided into two studies at two participating sites at Universitätshklinikum Schleswig-Holstein (UKSH), respectively at Campus Lübeck and Campus Kiel.

7.1. UKSH - The studies

The purpose is to test the usage of the Cortrium C3 device as an equipment tool for continuous monitoring of the health condition long-term and chronically ill inpatients by measuring three out of five vital sign parameters at 1) Department of Oncology and Hematology, Campus Lübeck, and 2) Department of Radiation Oncology, Campus Kiel. At both departments the patients are admitted with cancer diagnose. The patients are therefore acting as test subjects for all long-term and chronically ill inpatients.

At UKSH, patients are monitoring their temperature at home. It is often fever (≥ 38.0 °C) that triggers hospitalization. When the patient is hospitalized, the vital signs are measured, cf. the clinical practice – including pulse and respiratory rate. Both the pulse and respiratory measurement from the C3 device are selected for testing the data validation and functionality in the clinical setting. Furthermore, registrations of temperature will be included to examine the coherence
between the clinical registration (digital thermometer, rectal measurement) and the C3 registrations of the surface temperature and the ambient temperature.

7.2.1. The C3 device - Contraindications
There are no contraindications by using the C3 device; neither for patients, not for the healthcare personnel. The C3 device is monitoring the vital sign parameters heart rhythm (pulse), respiratory rate and body surface temperature without affecting, respectively the health condition or any diagnose acquired by the patient, or interfering with other medical equipment at the hospital.

7.2.2. Inclusion criteria's
The Clinical indicators for including patients in the trials are legally competent patients of both sexes that are receiving treatment of cancer at UKSH. To participate in the clinical trial testing, the patient must be admitted in a febrile condition (Body core temperature of $\geq 38.0 \, ^\circ C$).

To sum up, the inclusion criteria's are:
- Legally competent patients - i.e., patients considered able to understand the information given about the clinical trial
- Age 18 years or older
- Patient admitted to the hospital in a febrile condition (Body core temperature of $\geq 38.0 \, ^\circ C$).
- Patient has given a written informed consent

Exclusion criteria's are:
- Not legally competent patients
- Pregnant women
- Fertile women, who do not use contraceptives
- Patients under 18 years
- Patients with known heart-related disease

At The Department of Oncology and Hematology (Campus Lübeck) and The Department of Radiation Oncology (Campus Kiel), patients are mainly elderly persons above 55 years. As cancer does not under normal conditions affect the cognitive ability of the patients to evaluate their possible participation in the clinical trial. Thus it is, considered that only very few patients are excluded per se from participating in the planned clinical trials. The patients are informed, that participation is voluntary and that they can withdraw their consent at any time with no consequences for their further treatment. The patient is considered included in the clinical trial when the patient has both orally expressed and given written consent to participate. It is not possible to inform the individual patient in beforehand the hospital admission as the admission will have a spontaneous character due to the occurred febrile condition. For the individual patient, the clinical trial testing with the C3 device is considered finished when the vital sign monitoring with current equipment is finished - typically when the patient is sent home from the hospital.

All patients have the possibility at any time - in writing or orally - to withdraw from being a participant in the clinical trials. The Case Report Form will then be archived, and Cortrium won't have access to the monitored data from the patient. Thus, clinical data from patients who have decided to withdraw during the testing period will not be part of the data validation studies. Withdrawing patients won't have an effect on the overall number of included patients.

7.2.3. Patient data - which data is subject to analysis?
When the patient has given the consent to be included in the clinical trial, then the patient will start to be monitored with the C3 device. When admitted outside normal office hours (08.00-17.00 h), the monitoring will await until the personnel in the daytime arrives at the clinic. The following personal data will be noted by the nurse including the patient in the Case Report Form.
• Date and time for inclusion and termination of the testing
• C3 device - the identification number
• Gender (male/female), age, height and weight
• Diagnoses/chronic diseases (e.g. diabetes, COPD, other)

From the C3 device, the nurse is reporting the following shown data within the Cortrium app:
• Pulse
• Respiratory rate
• Body surface temperature
• Device temperature
• Posture of the patient (upright, lying down(back), lying down (stomach)

Cortrium and OKSH have signed a data treatment agreement that allows Cortrium access to all data including the patients’ Case Report Form (Exhibit 5). As the data is delivered to Cortrium in an anonymous form, Cortrium will not be able to trace the patient data to the individual patient. By signing the data treatment agreement, the parties are secured that the data analysis is performed according to data security legislation. To this extent, Cortrium is in compliance with the ISO Standard for Information Technology - Security Techniques: Information management - Requirements (EN ISO 27001:2013).

Variables in the data validation studies are the paired observed data measurements specified by the Cortrium app compared with the data values from the daily procedures and equipment of measuring the patients’ vital sign parameters. While the nurse is noting the values from the Cortrium app, he or she must simultaneously report the measurement as she would normally do with the help of medical equipment (e.g. pulse monitor, thermometer). Respiratory rate is measured by the nurse via counting the number of breaths for 30 seconds and then multiplied by two to get the breath per minute. The body temperature is measured with a rectal or ear thermometer. All measured data is written in the Case Report Form. A schematic overview is drawn below:

Table 6: Vital signs parameters measured in the clinical trial study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Current Clinical Practice (BOS-scoring)</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse /heart rate (beats per minute)</td>
<td>Pulse oximeter placed on finger</td>
<td>Derived from ECG-signal by use of Open Source analysis software</td>
</tr>
<tr>
<td>Respiratory rate (number of breaths per minute)</td>
<td>Measured at rest by counting the number of times the chest rises for 15-30 seconds. The rate is multiplied as equivalent to one minute.</td>
<td>Respiration signal is based on impedance changes measured between two ECG electrodes. The frequency is derived from fluctuations in the signal.</td>
</tr>
<tr>
<td>Temperature (estimate for core temperature in degrees Celsius)</td>
<td>Digital thermometer, measured rectal or in ear according to current guidelines for temperature measurement (Annex 5)</td>
<td>An IR thermometer on the sternum measures surfaces temperature. A digital thermometer placed in the C3 unit measures ambience temperature. Both sensors have 0.02 °C accuracy.</td>
</tr>
</tbody>
</table>

The health authority report form will be updated every time new patient consents to participate in the clinical trials. A template form of The Case Report Form can be reviewed in Exhibit 6.

7.2.4. The Case Report Form - Identification key
The identification key is a random code that is kept by the medical doctors responsible for the clinical trials at UKSH, respectively Prof. Dr. med. Dirk Rades (Campus Lübeck) and Prof. Dr. med. Jürgen Dunst (Campus Kiel). 30 days after the termination of the clinical trials, the
identification key code is destroyed so that recorded data can no longer be connected to the individual patient. In case the identification key get stolen or by mistake is transferred to 3rd parties, the responsible person must immediately inform Cortrium, the health authorities, and the ethical committee. Also, all Case Report Forms must be destroyed immediately. After these procedures, the clinical trial testing can restart.

7.2.5. Data validation studies - Thesis

The clinical trials at UKSH have exploratory nature characteristics. The data validation studies of the pulse, respiratory rate and infection consist of paired measurements of the vital sign parameters. The comparison is the current golden standard practice of vital sign measurements in the UKSH clinics. The C3 device measures pulse via the heart rhythm frequency, and the respiratory rate measurements are impedance based changes between two ECG electrodes combined with the accelerometer data for the height adjustable changes of the chest when breathing. The C3 device measures the body surface temperature and device temperature via an infrared thermometer embedded within the device. With all the monitored data brought together, the study is analyzing a possible new paradigm for infection.

All monitored data is accessible for the healthcare personnel via the iPad mini. On average, three times a day, the nurses will take all the vital sign measurements by using current procedures and equipment. When doing the vital sign measurement, the nurses will as well note the values for a pulse, respiratory rate, body and device temperature as stated in the Cortrium app. Every time the nurses are doing the procedures, it counts for one paired measurement.

Thesis 1 (pulse): The C3 device produces clinically validated pulse data.

Thesis 2 (respiratory rate): The C3 device produces clinically validated respiratory rate data (breathes per minute).

The paired measurements for a pulse and respiratory rate are analyzed by using difference plots (Bland-Altman plots). Outliers and systematic bias data can be analyzed. The data validation study will calculate and define a 95% "limits of agreement" (average difference ± 1.96 standard deviation). The calculation will tell the differences between the two measurement methods, respectively the C3 devise and the current procedure in the clinic. In case the difference is without clinical significance, the two methods can both be used in the future. Similar, there will be calculated estimates (Confidence Intervals) for the "limits of agreement".

The inclusion of 200 paired measurement (n=200) gives a 95% confidence interval on ± 0.24s (where s is the standard deviation of the difference between the two methods). The calculations are considered appropriate for the data validation studies.

7.2.6. Febrile patients and the C3 device body surface temperature

A patient in a febrile condition (≥ 38,5 °C) is an indication of an infection. Patients with cancer are monitoring their temperature at home. Very often fever (≥ 38,0 °C) is the triggering factor for admission to the hospital. The C3 device measures the body surface temperature where the C3 device is located on the sternum. In literature, there are no studies about a non-contact infrared on sternum measuring the body surface temperature. Nor is there any evidence in the literature about a possible correlation between the body surface and the body core temperature.

Relevant studies have been identified individually from references in other studies. A study from 1936 shows that skin temperature, in general, is between 33,5 °C and 36,9 °C, and that the skin temperature on the torso and the head are less influenced by ambient temperature sources. In a more recent study, the body surface temperature was measured 1,5 cm underneath the navel, and

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3 Bierman W. Temperature of the skin surface. JAMA, 1936; 106:1158-62
evidence showed that obese persons have significantly lower skin temperature than persons with normal weight.\textsuperscript{4} A direct relationship between skin and core temperature among adults is not described in the literature.

A review study identifies several challenges and assumptions about correlating the skin temperature to the body core temperature, e.g. the ventilation of the skin surface, the clothing, the ambient temperature, the body conformation, and the degree of vasodilation in the measured area of skin. The review article recommends that to minimise any bias's, a non-skin contact thermometer like the infrared thermometer in the C3 device, is recommendable.\textsuperscript{5}

A study performed with 167 children between 1-48 months has shown that infrared measurements on the forehead are strongly correlated with the rectal temperature ($r = 0.952$) and with sensitivity and specificity values of 97%, and negative predictive value of 99% for fever. It is not expected that the evidence shown with children is communicable to adults.\textsuperscript{6}

**Thesis 3 (Infection)**: With no justified statistical significant correlation between skin and body temperature, the study is exploring how to prevent aggravated or lethal outcomes of cancer treatment, e.g. chemotherapy, by using vital signs measurements combined with accelerometer data to detect infection levels.

If the clinical testing of C3 device finds a correlation between the measured data and the patient's core temperature, the study will be an innovative and pioneering breakthrough for new ways of measuring infection levels. Thus, the continuous body surface temperature measurements will be analyzed and compared to the data for heart rhythm, respiratory rate and accelerometer data.

### 7.2.7. Number of patients included

With the above statistical considerations regarding 200 paired measurements for the vital signs parameters, it is estimated that each C3 device must include ten paired registration (200 measurements/20 C3 devices = 10 paired measurements).

The following calculation is an estimate of how many patients that allegedly must be included in the project to achieve the required 200-paired measurements. The patients are hospitalized at two sites, respectively at Campus Lübeck with an approximately admission period of 7,75 days, and Campus Kiel with an approximate admission period of 13,1 days in Kiel. The patients have their vital signs monitored three times during the first day of admission, and at least once a day in the following admission days. With the above assumptions in mind, one patient included in the clinical trial at Campus Lübeck will generate $\approx 9$ paired measurement, and at Campus Kiel, an included patient will generate 15 paired measurements.

The ambition is to have 100 paired measurements from each hospital site.

Campus Lübeck - 100 paired measurements divided by nine paired measurements per patient = 12 patients

Campus Kiel - 100 paired measurements divided by 15 paired measurements per patient = 7 patients

It is assumed that 25% of included patients won't complete their participation in the clinical trials. Thus, it is estimated that approximately 15 patients will be included in the clinical trials in Lübeck, 12 patients will complete the testing period. In Kiel nine patients will be included, seven patients

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\textsuperscript{5} Taylor NA, Tipton MJ, Kenny G3. Considerations for the measurement of core, skin and mean body temperatures. J Therm Biol 2014;46:72-101

will complete the testing period. With 11 weeks as defined as the testing period, one or two patients must be included on average per week. However, it is the goal of 200-paired measurements all together in Lübeck and Kiel that determine the final number of patients included in the clinical trials. Based on the above statistical considerations to make 200-paired measurements for all parameters, calculations show that reuse of C3 devices is not needed. Each C3 device is only connected to one patient.

7.2.8. The protocol - Deviations
All procedure deviations from the clinical trial testing at UKSH will be reported to BfArD. It is a 2-step reporting procedure. 1) BfArD is contacted by phone about the procedure deviation(s), 2) The phone call is followed up by mail or letter where the procedure deviations are further explained and including if needed, suggested steps getting back to the originally planned procedures. It is BfArD who decides whether the procedure deviations require a new approval of a revised protocol - or if the deviations have minor impacts that allow for going on with the clinical trials.

7.3. The C3 device - Qualitative analysis
As part of the clinical trials at UKSH an ethnographic study is planned. The study investigates the challenges when introducing smart wireless technologies as tools for monitoring the patients’ health data. The study includes the evaluation, views and opinions from the healthcare personnel and the patients. The reason behind conducting the qualitative study is that on a global scale, 75% of the total health care costs are used in treatment and care for persons with chronic diseases, including cancer. The number of chronically ill persons with one or several diagnoses is increasing. The demographic development implies a considerable increase in the part of the population above 60+ years leading to increased health care costs in an already financially pressured health care system if new and smart technologies are not introduced.

7.3.1. The recruitment of patients and personnel for the qualitative study
Secondary to the actual testing of the C3 device on patients, the responsible nurse, respectively at Campus Lübeck and Campus Kiel, is in charge of recruitment of patients and healthcare personnel for the interviews. For preparation, research personnel from UCSJ and DSKD conduct ethnographic observational studies at the hospital departments during the trial period.

7.3.2. Background
New technology is seen as one of the future solutions of the demographic challenges for the healthcare system. In the Danish national telemedicine action plan, ”National handlingsplan for udbredelse af Telemedicin”, new technology is emphasised as a solution for care and treatment of chronically ill patients. New technology is assumed to benefit welfare including the everyday life for citizens as well as reducing admissions and re-admissions to hospitals. The optimistic views on new smart technologies are not necessarily shared by research. Often the introduction of new

7 http://www.oecd.org/health/
8 Lægemiddelstyrelsen. Det danske sundhedsvæsen i internationalt perspektiv. Lægemiddelstyrelsen, 2010
9 Vallgårda S, Krasnik A (red). Sundhedsøkonomi, Munksgaard 2010
13 Department of Health. Whole System Demonstrator Programme Headline Findings – December 2011
technologies does not have the expected gains on welfare by making the everyday life of healthcare personnel and patients easier. A necessary element in the proliferation of telemedicine solutions is the use of inexpensive and simple-to-use sensors for monitoring patient health data independently from a hospital setting. Some of these sensors are already widely used within fitness and self-tracking; also known as "wearable-tech", worn on the skin or within smart fabrics, and wirelessly connected to phones and tablets. Within the healthcare system, the term “mobile Health” or “mhealth” is an expression associated with the smart sensors.

**Figure 1: PubMed results distributed yearly on search for "Wearable" and "mHealth"**

![](image)

Attention in research to analyze the digitalization of healthcare is huge. Publications have accelerated in recent years (Figure 1).

### 7.3.3. Content and expectations - The qualitative analysis

UCSJ and DSKD are conducting usability studies of the introduction of smart sensor technologies. The clinical trial testing of the C3 device serves as a pilot test. But the investigations on the usability and the impacts on workflow in the hospital have a broader perspective. Many empirical studies are showing that the introduction of smart technology to healthcare personnel and their patients do not have the expected efficiency outcomes. According to the Danish national institute for municipal and regional studies, the acceptance of the users of technology equally important as the organizational set-up, users technical skills, and legislation for accomplishing the purpose of introducing new smart technological solutions. The

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16 Dudley L. Garner P. Strategies for integrating primary health services in low- and middle-income countries at the point of delivery. The Cochrane Collaboration. Published by John Wiley & Sons Ltd, 2011
The introduction of new technology is not a one-time magic solution to all challenges. It is a continuous process followed-up by adjustments and adaptation of new workflows and work tasks. WHO defines quality in the healthcare sector according to five parameters:

1. Efficiency in work resources
2. Efficiency in capital resources
3. Minimization of risk factors for the patients
4. Securing that patients are satisfied
5. Ensuring coherent solutions

With these WHO parameters in mind, healthcare is monitored and accredited according to the Danish quality standard (DDKM) with quality indicators such as healthcare provision, organizational and patient experience.

As healthcare provision is monitored according to health deliverables, the quality of new technological solutions must at least produce deliverables of the equivalent quality standard as of today. Thus, besides testing the data quality of the C3 device, it is essential to further explore the experienced quality among patients and the healthcare personnel when new technology, such as the C3 device, is introduced.

The C3 device anticipates the introduction of smart wearables-tech in hospitals. The qualitative study is focused upon:

a) How the patients and the healthcare personnel experienced the usage of the C3 device in the clinical trial.

b) Which challenges do the patients and the healthcare personnel experience in general when new technological solutions are introduced, e.g. how important are the necessities of introducing a new technological solution in the daily workflow?

The observational studies will be carried to discover and elucidate possible challenges related to treatment and care of patients, wearing the C3 device. The research team will observe routines and trajectories according to recommendations, as well as gain insight in the setting to qualify the implementation of C3 and the interviews.

The interview: Experienced researchers from the Innocan-Team will conduct the interviews. During the interviews a semi-structured interview guide will be used based on research themes emerged on the research literature on the topic. The interviews will be held in a relaxed atmosphere which allows the patients and healthcare professionals to speak freely and informative information on the topic will be shared. The researcher will guide the interview using the interview guide and ensure that all areas are being covered in the dialogue, yet allowing for spontaneous and informative descriptions on the phenomena that have been of importance to the informant. The estimated number of patients and staff members are 10 – 12 respectively, but inclusion will continue until data saturation is met.

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24 Stevnhøj AL (red.) Den danske kvalitetsmodel. Kvalitet i bevægelse. Institut for Kvalitet og Akkreditering i Sundhedsvæsenet (IKAS), 2014
26 Brinkman S & Tanggaard L: Kvalitative metoder. Hand Reitzels forlag, København 2010
The interviews will be digital audio taped and transcribed verbatim. The data will be collected according to the guidelines of Good Clinical Practice (GCP) for medical device studies. All data are anonymized, and all data are protected according to Danish National Law: “Lov om behandling af personoplysninger” (a law on handling confident personal information). The project has been reported to “Datatilsynet”.

Thesis 4 (Qualitative study) : The qualitative study is not addressing a particular thesis, nor is the study working with significance levels and the represent ability among healthcare personnel and patients. The study will report the advantages and disadvantages regarding new technological solutions, and the change in workflow and healthcare provision as it is experienced by the healthcare personnel and the patients.

7.3.4. Perspective regarding the collaboration with UCSJ and DSKD
UKSH envision that the collaboration with UCSJ and DSKD gives all parties a more comprehensive understanding of the benefits of introducing a new technological solution in the healthcare sector, e.g. improved capacity to select sensor technological solutions in the future. In the end, the quality, the safety and the flexibility for patients are highly prioritized. Thus, the clinical trial is pathing the way for introducing new sensor technology solutions at the hospitals in Germany and Denmark. The natural next step is a coherent medical technological assessment report.

8. The C3 device - Side effects, risks and disadvantages

8.1. The C3 device - The healthy volunteer test
The C3 devices are measuring pulse, respiratory rate and body surface temperature. The device has previously been tested on healthy volunteers. The study was conducted by the healthcare personnel at Næstved Hospital, Department of Oncology (February 2015). The purpose of the study was an evaluation of the C3 device regarding testing the device in clinical trials settings. 32 healthy volunteers participated in the testing (24 women, eight men). All participants were wearing the C3 device during a working day (≈8 hours).
The test report can be accessed (Exhibit 7). The main conclusions were as follow:
1. Data validation (pulse, respiratory rate, temperature):
   - The pulse measurements are evaluated as valid compared with counting the pulse at the wrist
   - The respiratory rate measurements were evaluated as not valid. After the testing, Cortrium has enhanced the own developed algorithm for calculating the respiratory rate. The new algorithm was processed and validated on the test data
   - The body surface temperature measurements were evaluated as not correlated with the body core temperature.
2. Experienced disadvantages
   - Only one person reported skin irritation for around ½ hour at one of the electrodes. After an ½ hour, the irritation stopped. No other participants reported any disadvantages regarding the C3 device.

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3. Identification of medical risks during the healthy volunteer study
- All 32 participants in the healthy volunteer test were wearing the C3 device for one working day (≈8 hours). No medical related risks were identified. Neither did any interference with other medical equipment occur during the testing period.
It was noted that the Bluetooth connection from the C3 device to the tablet (iPad mini) periodically was unstable. Nevertheless, the unstable Bluetooth connection had no interference with the storage of the data. All data was stored on the embedded memory card on the C3 device.

8.2. Conclusion - The use of the C3 device on patients
As mentioned in section 8.1., one person reported that the ECG electrodes produced irritation at one of the three electrodes adhered to the sternum. A discomfort comparable to the movement of a patch. The use of the C3 device is non-invasive. Besides the eventual discomfort with the ECG electrodes, it is evaluated that there are no side effects or risks connected to testing the C3 device on patients. In the event, the patient is irritated or develop an allergic reaction to a given ECG electrode; it is always possible to identify the type of electrode, e.g. from another manufacturer. The markets for electrodes are vast with many opportunities to identify an electrode suitable for the individual patient. The C3 device is CE classified as consumer electronics. It implies that the device is in compliance with the EU safety and health requirements.

9. Patient data - Ethical considerations
No biological material is collected as part of the clinical trials. So no authorization is needed to a biobank. It is emphasised that the clinical trials are conducted without Internet access. Data is stored on the C3 device and the individual iPads. Data transmission from the C3 device for iPads will be encrypted. Overall, the clinical trials are conducted in compliance with the Guidelines for "Good Clinical Practice" DS / EN ISO 14155: 2011 ", and the collected scientific data is handled in accordance with the“ Law concerning the processing of personal data.30

9.1. Interviews - Ethical considerations
In the qualitative study at UKSH, identifiable material such as the recordings of the interviews, the transcripts, etc. will be destroyed when the material is no longer needed. The regional research ethics committee in the Region Zealand (DK) has approved an identical clinical trial at the Danish hospital in Naestved, Department of Oncology. The approval is annexed as Exhibit 8.

9.2. Patient information
The patients who are offered participation in clinical trials are receiving written information about the trials. Also, all patients offered a detailed interview with an assessor, and all patients are encouraged contemplation time before their final decision. Consent can only be given by the patient. It is not possible for the individual patient to hand over the authority to decide to another person.
The participant information and the template patient consent form are annexed, respectively as Exhibit 9 and Exhibit 10. In addition, the participating patients have to sign a document (proxy statement) that allows the Medicines Agency and the relevant foreign health authorities' access to the patient records for inspection and control of the experiment. Template for the proxy statement (mandate) is annexed as Exhibit 11.

9.3. The use of patient data from the C3 device
Patient data from the C3 device is analyzed only in connection with the clinical trials. The data is

30 Cortrium is excepted from reporting that data will be processed by Cortrium when the data is produced during the clinical trial testing, cf. Bekendtgørelsen af 9. maj 2013 om undtagelse fra pligten til anmeldelse af visse behandlinger, jvf. §1 stk. 3. (in English: The Danish Legal Act of 9 May 2013 on exemption from the obligation to review certain treatments, see. §1, Section 3.)
not subject to any clinical decisions. The participation in the clinical trial does not lead to any delays in the treatment of the patient. The patients are throughout the admission to the hospital monitored by medically certified approved equipment. Only on the basis of data from the certified medically approved equipment, healthcare professionals can make decisions and diagnosis. Patients can at any time during the trial testing period withdraw his or her inclusion - without facing a deterioration of their planned treatment. The clinical decisions, All patients will continue to follow the treatment plan. The clinical trial will by no means bring forward or postpone any planned treatment by the healthcare personnel. On the submission date of the application to BfArD, no authorized access is given to other countries' health authorities.

10. The clinical trials - Organizational set-up (Quality Management and Control)

The clinical trials at Campus Lübeck and Campus Kiel are managed as one clinical trial taken place at two hospital sites (Investigators). Cortrium is coordinating the clinical trials with each responsible nurse at Campus Lübeck and Campus Kiel. Both sites are using the same medical equipment; the Cortrium C3 device.

10.1. Cortrium - Resources and infrastructure

Cortrium was established in autumn 2014. As of 1. November 2016 the company has six employees (one medical doctor, four engineers, one project manager). Together the team experience more than 90 years of professional work with smart technologies and medical equipment business. The management team at Cortrium consist of two persons. All documentation and communication are digitalized with restricted access only to the employees. As internal communication platform, the company uses Slack. Jira and GitHub are used for documentation of the developed versions of the technological platform including the Cortrium app. Cortrium owes all IP to all the products and services. All components are bought directly from manufacturers or distributors. Cortrium is assembling the C3 device once all the components, raw prints and shielding can is received from suppliers. The C3 device complies with all essential regulatory requirements, cf. the Medical Device Directive (93/42/EEC), except for the aspects covered by the protocol, and with regard to these aspects, all necessary precautions are taken to protect the patient's health and safety (Annex 4).

Cortrium has received venture investment in 3. Rounds, respectively from Bayer AG, Myant Capital Partners, and Area9 Invest. In total 1,6M€ is secured via investments. Annual turnover for 2016 is estimated to be 130K€. The investment rounds are covered further R&D on the vital sign platform and the process for regulatory compliance with the Medical Device Directive (93/42/EEC).

10.2. Cortrium - The Quality Management and Risk Management Systems

Cortrium has until September 2016 produced 250 units of the C3 device. All functioning C3 devices are registered in the Cortrium database including info about the lifecycles of the devices, hardware repairs, software versions, user history and comments, lent-outs and sales. The current C3 device is developed via eight iterations for securing the quality of the hardware.

As mentioned, Cortrium is already having sales on the current iteration of the C3 device to healthy individuals and for research purposes. Especially research and companies working with stress test have shown interest due to the high-frequency ECG sample rate (250 Hz). Thus, Cortrium has a quality and risk management system up running that is materially consistent with requirements for medical device manufacturers prescribed in EN ISO 13495: 2012 (Quality Management System - Requirements for regulatory purposes) and EN ISO 14971: 2012 (Application of Risk Management to Medical Devices). Entries in the database about customer feedback on design, user interface and unintended incidents of the produced C3 devices are also largely in line with the requirements of EN ISO 62366: 2015 (Application of Usability Engineering to Medical Devices).
10.3. The management of adverse events

Adverse events or near-adverse events are not expected to happen during the testing of the C3 device. The C3 device is non-invasive. The device is passive to the extent that the device is only monitoring vital sign parameters of the patient. No clinical decision will be taken related to the values shown or recorded by the C3 device. If an adverse event or near-adverse events occur, where the C3 device is the cause, these procedures will be followed:

- a medical assessment will decide how long the patient must be under observation
- the clinical trial testing will be suspended immediately

Attached to the protocol is the health authorities report form for adverse events (Exhibit 12). To ensure traceability and documentation, adverse events or near-adverse events must be documented in an independent annex to the Case Report Form. In case adverse events or near-adverse event occur, the health personnel must "freeze" the set-up to the degree that it is still safe for the patients, colleagues and other visitors. Nothing can be thrown out or removed when the adverse event has happened. Following the national legislation for research ethics (in Denmark Act no. 593 of 14/06/2011, §30), the health authorities and the ethical committees must be contacted immediately. Internally at both hospitals, the responsible physician must be notified immediately as well. As the C3 device can be traced to other patients that have tested the C3 device before, the investigator must track these patients and examine whether these patients have any side effects due to C3 device.

10.4. Patient data - unauthorized access to the identification key after the ending of the clinical trial

The procedures for unauthorized access to the identification key are not changed after the clinical trials even if the clinical trials have been terminated before planned schedule.

10.5. Campus Lübeck - Resources and infrastructure

This section must include:

- general description of UKSH, Campus Lübeck
- a specific description of the wards where the trial is taken place (number of beds, patient flow, patient characteristics (age, diagnoses, admission period, the number of beds, the number of personnel, etc.)

10.6. Campus Kiel - Resources and infrastructure

This section must include:

- general description of UKSH, Campus Lübeck
- specific description of the wards where the trial is taken place (number of beds, patient flow, patient characteristics (age, diagnoses, admission period, the number of beds, the number of personnel, etc.)

10.7. Conclusive remarks - Quality and risk management

As stated, Cortrium is already to some extent aligned with the international standards for quality management and control systems in production, records of devices, data management, etc. The ambition is to complete the clinical trials on-time, including the publications of end results with regards to legislation and clinically good practice. In case the protocol is changed, the health authorities and the ethical committee will be applied for a renewed approval, cf. Exhibit 13 (protocol amendment report form). When the clinical trials are finished, the health authorities and the ethical committee will be informed.
11. Financing
Cortrium has agreed with the participating hospitals that the hospitals have the daily responsibility of conducting the clinical trials in accordance with the protocol. This requires that the hospitals are financing the resources for:

- to contribute with relevant medical assistance to developing a protocol
- to contribute to the final report writing
- payment of fees to the ethical committee
- allocation of healthcare personnel (primarily nurses) for including and monitoring the patients with the C3 device
- to handle the patient reporting (Case Report Form)
- to deliver encrypted data files to Cortrium (the patient's Case Report Form)
- to be present in the event of an auditing by the national health authorities and/or ethical committee

Besides delivery of C3 devices, Cortrium has the following responsibilities for which Cortrium must allocate resources:

- payment of the fee for submission of an application to the health authorities
- provide technical support during the actual testing of the C3 device
- deliver user manual and procedures for the usage of the C3 device
- payment of expenditures related to statistical calculations and publication of results

12. Assurance
The participating hospitals are directly responsible for implementation of the clinical trials. Thus, both patients and healthcare personnel involved in the clinical trials of the C3 device are covered by the hospital assurance schemes, e.g. the Patient Insurance Scheme and hospital employees insurance schemes. Both insurances apply to participation in clinical trials and research projects.

13. Publication policy
The clinical trials will be the subject of scientific articles. Currently, the publication schedule is not known to the involved parties. The clinical trials have been notified at [http://www-clinicaltrials.gov](http://www-clinicaltrials.gov). Here, the thesis and other facts are listed before the commencement of the clinical trials.

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1.4. Exhibits - Overview

Exhibit 1a: Campus Lübeck - Clinical site agreement (Section 2.1.)
Exhibit 1b: Campus Kiel - Clinical site agreement (Section 2.2.)
Exhibit 2: The C3 device - manual. (Section 5.1.)
Exhibit 4: The manufacturers declaration about the C3 device (Section 6.2. & Section 10.1.)
Exhibit 5: Data Treatment Agreement between UKSH and Cortrium (Section 7.2.3.)
Exhibit 6: The Health Authority: Report form - Patient consent (Section 7.2.3.)
Exhibit 7: Kvalitetstest af Cortriums trådløse monitoreringsenhed C3 på raske testpersoner. Afrapportering UCSJ, 2. marts 2015. (Section 8.1. & Section 10.2.)
Exhibit 8: The approval from the Ethical committee - Region Zealand (Section 9.1.)
Exhibit 9: The participation information form (Section 9.2.)
Exhibit 10: The patient consent form (Section 9.2.)
Exhibit 11: Proxy statement (template) (Section 9.2.)
Exhibit 12: Adverse Events - Report form Health Authorities (Section 10.3)
Exhibit 13: Application form - Health authorities - amendments to the protocol.