Clinical tRials fOr elderly patients with MultiplE Disease

Final Report Summary - CHROMED (Clinical tRials fOr elderly patients with MultiplE Disease)

Executive Summary:
The CHROMED (Clinical trials for elderly patients with multiple diseases) project was designed and realized with the approval and the support of the European Community to improve follow-up of people affected by Chronic Obstructive Pulmonary Disease (COPD) and correlated comorbidities, such as Chronic Heart Failure (CHF) and Sleep Disordered Breathing (SBD). The aim was to assess changes in patient's health status and quality of life and to evaluate the socio-economic impact in terms of cost-effectiveness of a telemedicine-based platform to monitor respiratory and cardiovascular systems.

The CHROMED platform consisted of:
- Home Patient Monitor, used to complete daily validated questionnaires,
- RESMON PRO DIARY, a device for the home assessment of respiratory lung impedance using Forced Oscillation Technique (FOT),
- Wrist clinic Medic4all, delivered only to patients with severe cardiac comorbidities to measure blood pressure, saturation, body temperature and 1-lead ECG.

Time series of the measured parameters were automatically analyzed by specific algorithms and triggered cardiac or respiratory alerts that were sent to the clinical center taking care of the patient. Each medical alarm was followed by a nurse phone call to evaluate the patient status and in case of a confirmed worsening, plan a therapeutic action. To evaluate the impact of the intervention on the patient's status, quality of life and cost-effectiveness, questionnaires were submitted via monthly phone interviews.

An international multicentre randomized control trial (RCT) was conducted on 312 patients followed up for 9 months in five European countries: United Kingdom, Sweden, Estonia, Spain and Slovenia, representing different social and organizational contexts in Europe. Data on hospital accesses showed no statistic difference between the two study arms in time to first event, rate of hospital admission, and number of days spent in hospital. In total 7 subjects died during the study, with no significant difference between study arms.

There was not statistically significant difference between control arm and monitored arm in quality of life, clinical status and patient's depression at 9-month. Patients in the intervention arm had lower costs than the patients in the control arm, while there was no difference in QALYs between the study arms.
Subgroup analyses showed a significant difference (p=0.038) in the rate of hospital admissions compared to the previous year for those patients with at least a hospitalization in the previous year and a considerable cost savings for the healthcare system. A simple and accessible criteria such as having experienced an hospitalization for COPD exacerbation was able to successfully identify a population of patients for which the cost/effectiveness of CHROMED was maximized. Moreover, given that hospitalizations for acute exacerbation of COPD are the major contributor to the annual cost of COPD and that this is the most expensive chronic diseases found in elderly patients, the application of CHROMED in the EU healthcare services on the selected group of patients could lead to massive savings and better optimization of healthcare resources.

Project Context and Objectives:
Before CHROMED. Chromed arises from the results of a previous FP7 project experience (Chronic “An Open, Ubiquitous and Adaptive Chronic Disease Management Platform for COPD and Renal Insufficiency”) and the experience gained in the field of monitoring physiological parameters at home gained by RESTECH in a previous observational study focused at studying daily fluctuation of lung function in patients affected by COPD (Chronic Obstructive Pulmonary Disease).

Background. Age-related diseases have a major impact on today's society, with countries across Europe experiencing increasing financial and organisational pressures on their health and social security systems. According to WHO estimates, COPD affects 329 million people worldwide, nearly 5% of the global population. In 2011, COPD was ranked as the fourth leading cause of death, responsible for over 3 million deaths and over $2.1 trillion of expenses of the NHSs, resulting in a significant socio-economic burden. The number of patients affected by COPD is expected to increase according to the ageing of the population in developed countries.

Acute events are associated with exacerbations of the disease resulting in a dramatic worsening of the health condition of the patient and, in the most severe cases, to the patient's hospitalisation and administration of mechanical ventilation in intensive care units. It is estimated that up to 50% of the costs of hospital admissions for this group of patients could be avoided if there was appropriate home or community treatment that enabled earlier intervention (Wilkinson et al., 2004).

COPD is frequently associated with other chronic diseases such as cardiovascular disease (Feary et al., 2010) that affects health outcomes (Rutten et al., 2006). Chronic Heart Failure (CHF) is estimated to affect 23 million people worldwide, and the prevalence is increasing with an ageing population (McMurray et al., 1998). CHF is also one of the conditions commonly associated with COPD, being observed in about 20% of patients, and is the most common indication for hospitalisation among adults over 65 years of age (Graves, 1989). The rates of hospital admissions to treat CHF has increased progressively over the past two decades (Ghali et al., 1990) and readmission rates range from 29% to 47% within three to six months from the initial discharge (Gooding and Jette, 1985, Rich and Freedland, 1988, Vinson et al., 1990). CHF is therefore associated with high healthcare costs (Cline et al., 1996).

According to WHO reports, an effective COPD management plan includes four components: (1) assess and monitor disease; (2) reduce risk factors; (3) manage stable COPD; (4) manage exacerbations.

There is general consensus that home-based monitoring of elderly patients has the potential to improve patient wellbeing. To date, there is only limited evidence about the real effectiveness and efficiency of these approaches, particularly in the field of COPD and related co-morbidity. There are difficulties in obtaining a reliable and objective assessment of cardio-respiratory function without specially trained personnel (physicians, therapists or nurses) visiting the patient's home to supervise use of any technology. In addition, there is a lack of dedicated Information and communication technology (ICT) systems, capable of continuously collecting multiple physiological parameters and integrating these with clinical guidelines. Telemedicine-based care models that enable early diagnosis and treatment of acute events (exacerbations) are advocated to reduce the socioeconomic impact of chronic diseases. To appropriately monitor the conditions of patients with COPD and possible comorbidities, many physiological variables should be measured at home by patients.

Before the CHROMED experience, there were no existing telehealth systems able to objectively assess lung function abnormalities and early signs of exacerbation on a daily basis in COPD patients.

Many patients affected by COPD find it difficult to execute spirometry correctly when unsupervised (Miller et al., 2005), making spirometry less reliable when the patients use this tool for self-monitoring. Moreover, in patients with COPD, FEV1 is relatively insensitive to clinically relevant changes in overall lung function over short periods of time. This makes it highly reliable for ambulatory diagnosis but unreliable when used to early identification of acute respiratory events. Such factors help to explain why many previous studies evaluating home monitoring through spirometry or peak-flow meters have reported poor results (Brouwer et al., 2010). A promising technology for the home monitoring of respiratory diseases is represented by the Forced Oscillations Technique (FOT). FOT is a non-invasive method to measure lung function based on superimposing a high frequency (>4Hz) and small amplitude (2 cmH2O) pressure oscillation at the mouth of the patient during spontaneous breathing and, consequently, patient cooperation or supervision by specialised personnel is not required. In 2012 RESTECH, a spin-off company founded by the researched of the Respiratory group of the Bioengineering Department of the Politecnico di Milano University, developed a new concept of a home-monitoring FOT device based...
on this technology was developed, the RESMON POR DIARY.

CHROMED innovation. In the CHROMED project, lung function was monitored in COPD patients with comorbidities using an innovative technology that allowed the patient to self-collect data on his status in an easy and reliable way using the RESMON PRO DIARY device. These data, sent to the study server were used to identify a sustained deterioration and triggered a home call from a nurse that interviewed the patient and prescribed a treatment if deemed necessary.

CHROMED objectives. The CHROMED project was aimed to evaluate the effects of using a novel monitoring system to manage COPD patients with their usual comorbidities in order to optimize their treatment to improve their quality of life and reduce costs related to their health care.

The expected results of the project were:
1. A system easy to use and able to provide reliable data even in an unsupervised environment. This will be measured by computing the total patients drop-out for reasons related to technical issues identified by a specific questionnaire. A small drop-out will be considered satisfactory.
2. A validated clinical protocol and organisational model for telemedicine in COPD with common comorbidities (CHF, sleep disorders) with an accurate evaluation of impact in terms of both clinical and economic variables. This was the first study ever able to provide definitive data on such a large cohort of patients.
3. An increase of the time free from hospital admission for exacerbation
4. A reduction of disease-related costs.

From the users perspective the expected results could be translated as follows:
- Elderly patients receiving personalized care assistance, ease communication with doctors, continuous monitoring of their health status. That is, improvement in their quality of life.
- Clinicians enabled to assist elderly people from home, reducing hospitalization and exacerbation.
- Enterprises getting large scale validation, know-how development, improvement of the devices according to the users experience and international standards.
- Public health authorities finding new tools for the prevention of COPD exacerbation with a consequent reduction of costs for hospital readmission and visits, and improvements of the effectiveness of therapies.

Project Results:
CHROMED system. In the CHROMED project, an ICT platform developed in a previously funded FP7 project (i.e. CHRONIUS project) was adapted and used in combination with measurement devices and methods to monitor patients at home patients with COPD in combination with cardiac comorbidites. Due to the multidimensional nature of the diseases involved, the CHROMED monitoring system was designed as a complex modular multi-device architecture, composed by:

- Patient monitoring platform. A touch screen pc (Home Patient Monitor – HPM) represented the data collecting unit placed in the patient's home. Its functions were the following: 1) to share the 3G connectivity with the other devices assuming a gateway function, 2) to maintain a daily relation with the patient offering questionnaires and reminders for its daily prescribed activities, and 3) to allow remote connection to patient devices for support purposes. Information on patient's symptoms was collected through the completion of questionnaires (i.e. COPD, CHF, SRDB, EQ-SD, PHQ-9, MHLF, Cost, User satisfaction, etc.) translated in the local languages displayed daily in the HPM through simplified user interfaces. The system was also equipped with an innovative CE-marked device that implements the FOT for the measurement of lung function noninvasively (RESMON PRO DIARY) and, depending on the presence of contingent comorbidities, specific devices for the measurement blood pressures, oxygen saturation, body temperature, and 1 lead ECG (Medic4all Wristclinic) or ventilator patterns during home mechanical ventilation (CPAP monitor). A mobile modem allowed an easy access to the Internet for sending the data to a central database.

- Central server. The data acquired by the HPM were automatically sent, at the end of the daily measurement session, to a central database where specific algorithms run in real time to perform data integrity tests and specific filtering to reduce the generation of false alarms and increase the system accuracy to identify a patient's worsening. Then the data were processed according to specific clinical algorithms and medical alarms generated and sent to the clinical staff.

- Chromed clinician web platform. Data stored in the CHROMED central server and generated alarms were accessed by the Clinical staff in charge of the patient through a specific web interface. This information was then used to program the best treatment according to the patient's status. In particular, the clinician interface itself offered to the user the following functions: 1) alarms visualization and
operation, 2) medical data visualization, and 3) patient recruitment and operation. The alarm section enabled medical staff to quickly have an outline of the currently open alarms in the Chromed system. Using the platform medical staff could input additional data regarding the alarm, as well as change its state. The alarm section was the first section visible on the platform, mainly because the outcome of the CHROMED project was strongly dependent on the design of an effective alarm system that allowed an immediate action in case of worsening of the condition of the patient. Thus, a high level of accuracy on the alarm generation and adherence to management processes were the core of the project itself.

The monitoring system had to be able to detect exacerbations, commonly defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD. To meet the described specification, two levels of alarms were implemented:

- **Low Priority alarms**: generated on the first day of occurrence of a worsening of medical condition or in presence of technical problems. Unless the condition was still verified the following day, no action was be undertaken by the medical staff and the alarm was automatically closed.
- **High priority alarms**: originated from Low Priority alarms when the condition of worsening lasted for at least two consecutive days. Since they satisfied the persistency condition, High Priority alarms were managed by the clinical staff.

Specific management protocols for medical and technical alarms were also defined. Medical alarms were generated by:

- the ResmonPro, which detected variations in mechanical properties of the respiratory system. The algorithm for the exacerbations detection developed on the ResmonPro was based on the detection of a persistent trend of worsening on specific parameters. As a consequence, each RESMonPRO alarm was an High Priority alarm;
- the Medic4All (when provided), which evaluated a worsening in the cardiac conditions of the patient (i.e. blood pressure, saturation, ECG, HR, and Temperature). Medic4All alarms were generated when at least one of the parameters under monitoring crossed a specific threshold.

When a new high priority medical alarm was generated, the staff in charge of the patient had to handle it as soon as possible, by following the chart of intervention: 1) contact the patient and ask, in a neutral way about his/her conditions; 2) if the patient reports a worsening in his condition, symptoms description is required; 3) then the caregiver will evaluate, according to the guidelines of his NHS, if a treatment is necessary; 4) if the patient does not perceive any worsening, or the caregiver does not consider necessary a treatment, the patient must be advised to call back in three days in case any symptom emerges.

Moreover, to keep an high adherence of patients to the protocol a system of technical alarms was implemented to identify the presence of missing data. If data were missing for two or more consecutive days a high priority alarm was generated and the clinical staff was required to call the patient and gather information about the event and plan a solution.

The medical data visualization section allowed to view all the available medical measures and information per-patient basis. Search and sorting functions were realized as well as all data could be easily plotted by simply clicking on it. A section of the study portal enabled pilots to enter recruitment information, which were validated for formal correctness as well as for meeting the project recruitment criteria. As soon as the patient recruitment sheet was completed and verified, the patient was automatically randomized using a randomization sequence previously generated and embedded in the study platform and the result immediately visible to the medical staff. Randomized patient was then setup to start the study and medical devices provided when applicable, i.e. for operational patients. Patients’ state could be turned to paused (e.g. holiday break, etc.) or to hospitalized, so that the alarm system did not expect prescribed measures in those periods; when patients concluded the study, their state was marked as stopped that.

Even if the project used components already available on the market or previously developed, several changes were done to match the established platform design. During the first months of the project, technical partners were involved in the implementation of CHROMED system, by adapting and customizing the already existing platform to the project needs. Technological standards and relevant legal and ethical issues were analyzed in order to safeguard adequately all parts involved in the implementation and use of the CHROMED equipment.

CHROMED devices built up a secure overlay network over the Internet using VPN technologies and joining TESAN private network on a CHROMED subnet especially assigned for the project. This choice provided a high level of security, since every transmission of the project data could happen only on the secure VPN channel. Moreover, the communication with the HPM devices was bidirectional, allowing remote assistance and prompt debugging on error. Communication protocols used in the CHROMED project were based on Web technologies such as SOAP web service messaging, XML data format and HTTP/TLS data communication protocols. Several technical testing were implemented to assure the correct equipment running before its installation at patients home. Delivery of CHROMED systems was supported by training to the clinical personnel and user manuals.

**Testing protocol.** The study comprised 2 phases:

- **Phase A**: a feasibility study in 3 pilot centres (Uppsala, Lincoln and Barcelona) to determine the data quality, technical and training
issues associated with use of the system in the patient’s home.

- Phase B: a randomized control trial (RCT) in 6 pilot centres (Liverpool, Tallinn, Barcelona, Uppsala, Lincoln, Sezana).

The clinical protocol was designed, finalized, submitted to local Ethics Review Boards in each centre and gained approval.

The study centres screened for suitable patients according to the following criteria:

- Age: patients aged ≥60 years of age with a preference for those older than 65 at screening visit.
- Severity of COPD according GOLD guideline criteria (GOLD 2007). Patients are in GOLD grade II or higher and had a prior history of exacerbations and/or an hospitalization for COPD in the previous year and will have one or more documented non-pulmonary chronic conditions such as:
  - CHF due to left ventricular systolic dysfunction (LVSD) confirmed on echocardiography. CHF diagnosis is verified based on routine clinical investigations elsewhere within last 10 years prior to inclusion to the current study. Severity of CHF will be measured using the New York Heart Association (NYHA) classification
  - Sleep Disordered Breathing (SDB) identified by respiratory sleep studies or polysomnography according to the usual diagnostic practice of the center. Recommended diagnostic criteria for OSAS include AHI (i.e. Apnoea Hypopnoea index) ≥5 by polysomnography and evidence of disturbed or unrefreshing sleep, daytime sleepiness, or other daytime symptoms.
  - Co-morbidities based on a clinical diagnosis of ischaemic heart disease and/or hypertension or hyperlipidaemia either undiagnosed or treated.
  - Obesity/hypoventilation syndrome
- Tobacco use: Subjects with a current or prior history of ≥10 pack-years of cigarette smoking at screening.
- Subjects capable of providing signed written informed consent
- Subjects capable to perform study procedures and use the Resmon Pro at home.
- Subjects must have reliable mobile phone coverage at home

Exclusion criteria:

- Other diseases/abnormalities: Any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study. Patients with significant vision disturbances and mental disease will be excluded. Patients with serious co-morbid conditions contributing to their impaired functioning will NOT be excluded provided they meet the criteria above.
- Subjects that, at the recruitment, will have a planned prolonged absence (more than 10 subsequent days) from home during the study period.

During phase A (May 2013 – July 2013), a total of 16 out of planned 20 subjects were recruited. One patient abandoned the study at the beginning of the monitoring period because of clinical problems. The remaining 15 patients were monitored for at least three weeks, and their data used to assess patient’s compliance with the system, identify installation problems, infrastructure issues.

Results and feedback from phase A were used as input to improve the Chromed system and alarms management before phase B starting.

Phase B started on October 2013 till March 2016. The Chromed trial was designed as a randomized controlled clinical trial (RCT), meaning that the effect of the intervention (i.e. the monitoring platform) have been evaluated in terms of differences on study outcomes between an interventional group and a corresponding age-matched observational group. Patients were assigned to each group in a randomly to eliminate any possible bias arising from a selection of the patients by the enrolling centre. To this purpose a randomization system has been implemented on the web platform that automatically assigned each patient to one of the two groups according to their comorbidities. The system was based on a random sequence that has been generated by RES using specific statistical tools and associated to the patients’ codes. The correspondence between the codes and groups is not known by the clinical centres.

Phase B trial was split in two runs (RUN 1 and RUN 2) of nine monitoring months each.

Patients in the Monitored arm were requested to perform the following daily measurements:

- Lung mechanic using RESMON PRO FULL device
Symptomatic questionnaires
Cardiac parameters using the Medic4all device (only patients with cardiac comorbidities)

Patients in the Control arm were not provided with any device and were requested to complete daily a paper version of the symptomatic questionnaire and to send them to the clinical center at the end of the study period.

All the patients enrolled in the trial were contacted by phone for the administration of the following questionnaires:

Every 3 months:
- COST
- EQ5D

Every 2 months:
- CAT
- PHQ9
- MHLF (only patients with cardiac comorbidities)

At the end of the trial, the patients were requested to complete a satisfaction questionnaire.

Each clinical centre participating to the clinical trial implemented the procedure to train included patients for using the Chromed platform, to perform the platform installation at patients’ home and to perform the follow-up the patients included in the study.

Technical assistance. Chromed was an ambitious and demanding project from the technological point of view, as it required a high level of commitment both for patients, who had to learn to use the platform, and for clinical staff, who had to get familiar with the assembly of the equipment. Hence, technical assistance must be guaranteed and provided in the shortest time possible.

Assistance meant constant support in planning, installation, training, troubleshooting, maintenance, upgrading and disposal of the system.

The Chromed assistance approach, both in phase A and phase B, was systematic, evidence-based and designed based on consultative needs assessment and prioritization.

To overcome languages barriers, each study centre identified a local centre as interface between technical partners and patients/installled system. Training meetings were organized in loco with the personnel involved in the Chromed installation and patients monitoring. User manuals were provided.

Technical partners supported pilots during the trial by offering their assistance and providing ad hoc solution in the shortest time possible through two main channels:
- VPN connection that allows remote access to the HPM, in order to check its internet connection options, to update the software and verify its settings.
- Skype calls or Whatsapp messaging to guarantee real time support during the home visits and images exchanges.

Once issues was solved, the adopted solutions were spread to all the involved sites to increase the consortium awareness and improve quality, effectiveness, and efficiency of Chromed monitoring procedure.

Non-medical alarms were constantly monitored and analysed as support of the technical assistance experience to better understand the system behaviour.

According with the study protocol, each patient in the monitored arm was requested to assess his/her respiratory and cardiac function daily using the CHROMED monitoring system. The results of these measurements were immediately sent to the study server and a medical alert generated if at least one condition was met.

Data Analysis. The objective of data analysis was the evaluation of the recorded data aimed at monitoring data quality and identifying possible confounding factors.

The following activities have been performed:
- Design and implementation of a software platform for use of algorithms for incremental data processing. An off-line system for additional data processing was implemented as a tool to process and optimize data with more flexibility and computational accuracy.
- Data analysis of phase A. Data acquired during the pilot study has been analysed to identify possible problems in data quality and patient compliance. This activity has involved the download and analysis of RESMON PRO and Medic4all data, together with the patients’ answers to the symptoms questionnaires and resulted in a set of indications of use of the platform to be used during B to improve data quality. Moreover these data have been used to evaluate day-by-day variability to optimize the thresholds for alarm generation.
- Tuning of the COPD exacerbation algorithm. Using the data acquired during phase A, the algorithm for the generation of medical alarms because of patient’s worsening has been tuned according to the observed day-by-day variability.
- Incremental data processing during phase B. Using the data stored on the project study site, periodic monitoring of subjects compliance and alarms management status was performed. The project group conducted analyses on the following data:
- quality of the collected data,
• baseline characteristics of the population,
• analysis of the generated medical alerts and their treatment,
• number and length of hospitalizations,
• patient's quality of life and other outcomes,
• cost-effectiveness.

Results. Quality of the data was evaluated in terms of the number of received data compared with the number of expected measures while the patients participated to the trial. The analysis showed a high level of completeness of the data collected along the RCT. This applied to registration of daily measures via the CHROMED platform (for the patients in the Monitored arm), to the use of the paper-based diary (for the patients in the Control arm), as well as to all the questionnaires submitted to the patients every 2 or 3 months. Between November 2013 and June 2015, 312 patients were enrolled in the study, of which 154 were assigned to the monitored group and 158 to the control group. Block randomization effectively produced two well-balanced populations with similar baseline anthropometric characteristic, spirometric profiles, history of exacerbation, history of hospitalizations, severity of COPD, and comorbidities distribution. Subjects had a median age of 71 years, a post bronchodilator FEV1 of 49.8 %predicted, 41% had one hospitalization in the previous year, 61% had two or more exacerbations in the previous year, and 47% has CHF and/or ischemic heart disease.

Overall, the CHROMED monitoring system generated a median respiratory alarm rate of 0.55 alert/month/patient and a median cardiac alert rate of 7.06 alerts/month/patient. A high priority medical alarm triggered a phone call from the clinical staff to the patient to verify his/her status. Patients reported at least one symptom in 50% of the respiratory events. After interviewing the patients, the clinical staff deemed necessary a medical action in 34% of the respiratory worsening event. In 47% of the cases the clinical staff acted pharmacologically either by modifying the current drug therapy or prescribing antibiotics. In 34% of the cases a visit was deemed necessary and only in 3% of the cases the subject was hospitalized. Regarding cardiac events, the clinical staff deemed necessary a medical action in 37% of the cases. Differently from respiratory events, in only 26% of the cases the clinical staff acted pharmacologically either by modifying the current drug therapy or prescribing antibiotics, while 45% of the prescribed treatment consisted in a physician visit. In 8% of the cases the subject was hospitalized. Data on hospital accesses (hospitalizations, ER admission, and hospital-at-home) were extracted from hospital records for all the enrolled patients and the following information were collected: date and department of admission; date and department of discharge; primary diagnosis; secondary diagnosis. Each hospital access was examined by the scientific manager of the study and classified based on its diagnosis as a RESPIRATORY, CARDIAC or OTHER event. A large number of subjects (71% of the monitored group and 74% of the control group) was never admitted during the trial. No statistic difference was observed in the time to first event between the two study arm. No significant difference in the rate of hospital admission neither in the number of days spent in hospital between the study arms was visible. In total 7 subjects died during the study, with no significant difference between the two study arms.

Comparison of the results for the utility scores and EQ-VAS at 9-month did not show any statistically significant difference in the quality of life between control arm and monitored arm. Similarly, there were no statistically significant differences between control arm and intervention arm for the clinical status measured with the COPD Assessment Test (CAT), the Minnesota Living with Heart Failure (MLHF), and patient's depression measured via the PHQ-9 questionnaire. None of the sub-analysis showed statistical significant differences between control arm and intervention arm for the categories of patients with high-risk at baseline.

On average, patients in the intervention arm had lower costs than the patients in the control arm over the 9-month follow-up period. There was a reduction in the rate of hospitalizations for the patients in the intervention arm, which led to a cost saving of €1,323 in respect to those control arm. This difference, however, was not statistically significant (p=.110). All cost components related to hospital and primary care were lower in the intervention arm, with the exception of outpatient visits and use of ambulance. There were no statistically significant differences for any of the cost components.

A cost-utility analysis (CUA) with the perspectives of the healthcare system was performed to measure whether the intervention was cost-effective in terms of cost per quality-adjusted life year (QALY) gained. Overall the costs of the hospital resources accounted for €3,315 and €2,040 for the patients in the intervention arm and control arm respectively. Primary care resources accounted for €1,513 and €1,398 for the patients in the intervention arm and control arm respectively. This cost savings for the patients in the intervention arm balanced the additional costs required to provide them with the CHROMED platform and to follow them up remotely and managing medical and technical alarms. Over the 9-month period there was a differential QALY of 0.006 between the study arms (.491 versus .485; P= .731). The mean cost for the patients in the intervention arm was lower than that in the control arm (€4,831 versus €4,870; P=.816), although statistical significance was not reached. Therefore, patients in the control arm gained 0.006 QALYS more than those in the standard arm, with an additional cost of €216 per patient over the 9-month study period.

Subgroup analyses showed a significant difference (p=0.038) in the rate of hospital admission compared to the previous year between the two study groups for those patients with at least a hospitalization in the previous year (n=128) that was reflected a reduction of healthcare costs of 1734€/patient over the 9 month period. This saving comprises the actual cost of the prototypical equipment, the
Potential Impact:
Potential impact. With 312 patients enrolled and studied for 9 months by 6 clinical centers in 5 EU Countries, CHROMED is the largest international multi-center randomized control trial evaluating the effectiveness of an integrated telecare approach for COPD patients based on telemonitoring of physiological parameters.

The first relevant result of the CHROMED trial is that, with a proper design of usability of the technological platform and real-time management of patients’ adherence to the protocol, it is possible to reach extremely high adherence rates from this group of elderly chronic patients. The organizational model developed in CHROMED allowed to get reliable data from, in average, more than 90% of the monitoring days, a very good result compared to similar smaller studies (Ulrik et al., 2016).

Even if the equipment used for the trial is still in a semi-prototypical stage of development, with cumbersome components and a degree of reliability significantly lower than for commercial devices, the system was very well accepted by patients and the drop-off rate as well as the number of good quality measurements of lung mechanics was high when compared to other telemedicine trial in COPD.

It is also remarkable that the self-assessment of lung function by the new device based on the forced oscillations technique (FOT) provided higher reliability compared to the other physiological measurements in the trial (details in D7.1). CHROMED, therefore, clearly demonstrated that FOT can be successfully used for unsupervised monitoring of lung function, providing the first method for assessing lung mechanics outside the Pulmonary Function Test Laboratories and opening new opportunities for the diagnosis and management of lung diseases.

Despite the CHROMED system was still in a prototype version, with a number of technical problems occurred during the follow-up period, the positive results on the ease of use of the equipment will facilitate its future use in a routine clinical practice. Particularly appreciated was the contact with the health personnel. Remote contacts via telemedicine were considered as safe and satisfactory as face-to-face contacts. A routine use of the system by hospitals for disease management of patients with chronic diseases will thus represent a feasible, viable and convenient supplement to traditional outpatient care.

In our global patient population, the expected reduction in the time to the first exacerbation was not demonstrated. Interventional arm patients had a non statistically significantly shorter time to the first exacerbation compared to the control group. Data showed that the interventional arm patients had a non-significant reduction in the number of hospitalizations and days of hospital stay, suggesting that CHROMED allowed an earlier clinical management of the exacerbations, leading to less severe events with less need to hospitalization and, when hospitalization was necessary, leading to shorter hospital stay.

The lack of statistical significance of this trend has to be interpreted in view of the patient's characteristics in our study. Even if the inclusion criteria were defined in order to include mostly severe COPD patients with frequent exacerbations, almost 50% of the patients recruited were classified as GOLD stage II. As a result, severe and very severe COPD (Gold stage III and IV) provided 70% of the overall hospital admissions and 73% of the night stays.

This heterogeneous group of patients allowed to perform a subgroup analysis with a well-balanced groups size. This analysis revealed that patients that were hospitalized the year before the study (n=128) are responsible for 60% of the hospital admissions and 73% of the hospitalization days. When limiting the analysis of this group of patients, a statistically significant reduction of the hospitalization rate was found the monitored and treated with the CHROMED platform group, suggesting that telemonitoring of elderly COPD patients is effective only when applied on a selected group of severe patients.

It is remarkable that a simple and accessible criteria such as having experienced an hospitalization for COPD exacerbation is able to successfully identify a population of patients for which the cost/effectiveness of CHROMED is maximized. Moreover, given that hospitalizations for acute exacerbation of COPD are the major contributor to the annual cost of COPD and that this is the most expensive chronic diseases found in elderly patients, the application of CHROMED in the EU healthcare services on the selected group of patients could lead to massive savings and better optimization of healthcare resources.

Dissemination. Dissemination was an horizontal activity, undertaken throughout the life of the Chromed project. The main objective of the Chromed project dissemination was to provide the potential target audience with information regarding the project research activities, findings, results, and outcomes. The audience included healthcare providers and decision makers, as well as national and regional decision makers, the international research community, stakeholders (patients association and clinicians) and the media subjects.

Dissemination activities were also used to establish the market opportunities and to prepare the target audience for the promotion of the product. The project dissemination activities were directed to establishing the grounds for a possible, future commercialization of
the Chromed system.

Specific objectives of the project dissemination were defined in the following points:

- to achieve general public acceptance and agreement for the project;
- to continuously inform and present project activities and results in order to support the exploitation activities of the consortium partners for the future;
- to provide information to create and increase a public awareness of the project, its objectives, results, and benefits in all presumed target audience groups;
- to support the launch of the Chromed system and the development of its activities;
- to support the business plans and exploitation activities that would ensure a smooth introduction of the project results into the market.

To achieve the goal a series of activities were realized in three phases:

1) Phase 1: Initial Awareness/Intra-Consortium Phase: the objective was to create an initial awareness in the healthcare field:
   - producing of the Chromed logo
   - establishing of the Chromed website to provide general purpose information about the project's objectives, goals and major results
   - agreeing upon a dissemination strategy and future activities and monitoring relevant literature, resources sources and events.

2) Phase 2: Targeted Awareness/Market Testing Phase: the objective was to inform the selected target market about the characteristics and benefits of the Chromed system:
   - produce a newsletter,
   - publish a project brochure,
   - organize demo sessions
   - present the system and the project at the possible study population creating events for a wider audience (i.e. TV clips, articles published in the popular press, health promotion stands in city centre or at supermarket).
   - participate in public events
   - publish Chromed idea and preliminary results on scientifica papers

3) Phase 3: Product Launch/Implementation: the objective was to “maximise” target market and industry awareness regarding the Chromed results and proved benefits:
   - update newsletter
   - update Chromed website
   - participate in public events
   - publish Chromed results

Public events were carefully monitored and identified. The participation to these events happened in different ways:

- Direct participation with the lecture during the event
- Direct participation on discussion with experts
- Direct participation with project’s materials (brochure, poster etc.)
- Direct personal participation

Most of them were conferences, workshops or congress with an international outlook.

Several articles and project abstracts were published in professional newspapers, magazines etc., in order to grant a better availability to the general public and specialists.

In particular, abstracts of the interim data analysis and preliminary results of the project Chromed were presented at the 9th International COPD Conference (Birmingham 2014), at European Respiratory Society annual conference 2014 and on European Respiratory Society annual conference 2015.

Chromed web site was an essential dissemination channel both internally among the consortium members and externally supporting the clustering activities.

The CHROMED website has been running and updated during the whole project time. After a first version that was published at the beginning of the project, a re-styling of the website was done to be more attractive and highlight the main project information through a new more readable menu.

Chromed website has been used by the CHROMED Consortium for the following purposes:

- dissemination of up-to-date project information;
- storing dissemination documents in a project library;
- providing communication channel both internally among the consortium members (private access) and externally (public access)
supporting the clustering activities.

The web site is structured in the following main sections:

- Current Project Status, describing the trial status and the news related to the project development
- Project Description, with a summary of the project, its context and objectives
- Project Numbers, with the main details on project funding
- List of Project Partners, including a link to their own institutional websites
- Newsletter, containing a pdf downloadable version of newsletter
- List of dissemination activities, with a link to the full articles or to the downloadable version (where possible)
- Cookies policy, an information page in compliance with art. 122 paragraph 2 of the Italian Legislative Decree no. 196/2003 and according to the simplified procedures for the information and acquisition of consent for the use of cookies published in the Official Journal of the Italian Republic no. 126 dd. 3 June 2014 and in the Register of Measures no. 229 dd. 8 May 2014.

Deliverables and project documents were uploaded on the Consortium Common Area in order to ensure the availability also after the project ending.

The Intranet section is accessible via a username and password through menu items. For each Consortium participants are delivered personal login keys. The documents are organized in a usual way and accessible via a tree, whose structure is maintainable by the system administrator. All users are also content administrators so they can download stored files or can upload new files or remove them once positioned in a "leaf" node.

The project website will be keep alive for at least 2 year after the project ending in way to share the project results.

To foster the awareness of potential stakeholders of CHROMED scientific and technical impact the results of the trail a main manuscript resuming the main results of the study will be written and sent to a major international peer-reviewed journal of respiratory medicine by the end of 2016. To this purpose the protocol was registered on a public trial repository (clinicaltrial.gov). A consortium publication policy was defined among the Consortium for the dissemination of project results for 2 years after the project end to promote the publication of results on secondary analyses. A publications committee (Project Manager – Scientific Manager – Technical Manager) will coordinate publication strategy. Primary paper will be presented with 2 authors from each partner; full acknowledgment of all other participants. For the preparation of Secondary papers, a brief proposals (1 A4 page) has to be sent to the Publication Committee indicating the aim of the study and which data will be analyzed. Publication Committee will prioritize the project and discuss with the proposers how best to proceed. Secondary papers authorships will reflect the authors contribution but will normally include at least one author from each partner.

Exploitation. The exploitation strategy had two mains objectives

- to establish a clear business framework for commercial operation of the Chromed system, integrate this framework into the existing businesses of the Chromed partners and dynamically introduce the Chromed system into the marketplace;
- to draw an economic impact report for the system's usage by patients.

Specific activities were implemented to fulfill the exploitation objectives:

- analysis of Chromed scope in terms of:
  - boundaries of the functionalities that are covered by the Chromed platform and determine a specific positioning on the market;
  - critical success factors that are those performances in which it is important that the Chromed platform excel for competing on the market;
- market analysis in terms of:
  - potential population (COPD, comorbidities, etc.);
  - organizational models for chronic patients;
  - organizational models for telemedicine services;
  - existing reimbursement schemes for telemedicine services;
  - results from the cost-effectiveness analysis to estimate costs and savings deriving from the implementation.

A cost-utility analysis was performed to measure whether the intervention was cost-effective in terms of cost per quality-adjusted life year (QALY) gained. The results from cost-utility analysis showed cost savings of €1,275 in use of hospital resources for the patients in the intervention arm compared to the control arm. Costs savings for use of primary care resources accounted for €115. Overall, the mean difference for utilisation of healthcare resources from both hospital and primary care was €1,390. This cost savings for the patients in the intervention arm balanced the additional costs required to provide them with the CHROMED platform and to follow them up remotely and managing medical and technical alarms. Over the 9-month period there was no difference in QALYs between the study arms. The sub-analyses showed that there were higher cost savings for those patients with a previous history of hospitalizations. The CHROMED system seems therefore to be especially cost-effective for the patient at a higher risk of rehospitalisation. For future use in
clinical practice, hospitals are recommended to use the CHROMED system especially to those patients at high risk, identified with a previous history of hospitalizations. For each country additional data on the potential population who could benefit from the use of the CHROMED platform were collected. Moreover, information on existing national reimbursement schemes for telemedicine were also investigated and different scenarios regarding the delivery of the service through the public system with a reimbursement, or its commercialization were identified. At the moment, national reimbursement schemes for telemedicine are still absent in most European Countries. Therefore, hospitals will not receive any reimbursement from the national system for using the CHROMED system to remotely monitor patients with COPD. However, the positive results from the economic evaluation and the high cost savings generated for those patients in the monitored arm compared to those in the control arm make the CHROMED system an interesting future model of care in clinical practice. Moreover, the system can be a tangible option for health insurances programs focused on elderly ex-smokers with COPD and comorbidities.

List of Websites:
Project web-site:  www.chromed.eu

The coordinating partner is ELETTRONICA BIO MEDICALE s.r.l. The Company has broad international background, appropriate infrastructure, access to all the skills and technologies required to conduct a project in terms of management familiarization and tools, medical expertise, communication networks and systems engineering. The Project Coordinator is Dr. Eng. Roberto Rosso.

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The Chromed consortium covers a broad range of research and development competences covering clinical research, industrial development and end-user services.

RESTECH SRL – SPIN OFF DEL POLITECNICO DI MILANO (Italy)  www.restech.it

THE UNIVERSITY OF LIVERPOOL (United Kingdom)  www.liv.ac.uk

TALLINNA TEHNIKAULIKOOL (Estonia)  www.ttu.ee

UNIVERSITAT DE BARCELONA (Spain)  www.ub.edu/web/ub/ca

UPPSALA UNIVERSITET (Sweden)  www.uu.se

UNIVERSITETSSYKEHUSET NORD-NORDGE HF (Norway)  www.unn.no

UNIVERSITY OF LINCOLN (United Kingdom)  www.lincoln.ac.uk/home

BOLNISNICA SEZANA ZAVOD (Slovenia)  www.bolnisnica-sezana.si