



## Key points

- ▶ COPD is the fourth-largest cause of hospital admission as primary diagnosis, and a high proportion of patients are admitted through the emergency room as unplanned hospitalisations.
- ▶ In recent years, new strategies of patient empowerment and alternatives to hospitalisation have aimed to decrease admissions and reduce the burden on healthcare services.
- ▶ As the prevalence of chronic disorders increases, a holistic approach to disease management, involving patients, carers and all levels of healthcare provision, is needed in order to improve prognosis.
- ▶ A major project is under way in three European countries to prepare for the widespread introduction of information technology-dependent integrated care services.

# Integrated care for COPD patients: time for extensive deployment

## Summary

An ageing population and changing lifestyles are increasing the burden of chronic diseases, among them chronic obstructive pulmonary disease (COPD). To reduce the impact on patients, healthcare systems and society as a whole, a new, integrated model of care is needed. This must bridge the gaps between strata of healthcare provision, and empower patients and carers. It must cover all aspects, from prevention and early diagnosis, through personalised care plans all the way to end-of-life care.

A number of pilot studies have begun to address these issues, and a new European project aims to move towards a wider implementation of such a model, using information and communication technology (ICT) to link stakeholders at all levels. If such initiatives are successful, we can hope for a brighter future for COPD patients, and a lighter burden for society.

## Crisis management to integrated care

COPD is a leading cause of morbidity and mortality that generates a significant burden on healthcare systems worldwide [1, 2]. Despite recent progress in the understanding of the disease mechanisms and in treatment standardisation [2], severe exacerbations continue to be the major cause of unplanned hospitalisations in COPD patients, particularly in those in the advanced stages of the disease [3]. This phenomenon is partly explained by the impact of commonly associated comorbidities and poor social circumstances on COPD outcomes [4].

A recent analysis of the burden of all chronic conditions on tertiary care hospitalisations shows that COPD is the fourth-largest cause of admission as primary diagnosis [5]. But the impact of the disease is even higher in chronic patients with multiple annual admissions. The study indicated that, unlike patients

with cancer, patients with COPD or cardiac disorders were mostly admitted through the emergency room as unplanned hospitalisations.

It is well known that cardiac diseases, COPD and type II diabetes show a high degree of clustering [6–8]. Moreover, there is an unacceptably high rate of readmissions in patients with chronic disorders [9]. Taken together, the data indicate the need for re-examining the management of COPD patients who have exacerbations, in order not only to enhance the efficacy of care during exacerbations, but also to prevent admissions due to severe exacerbations in frail patients.

In view of the high social and economic burden generated by COPD hospitalisations, new strategies aiming to decrease admissions through patient empowerment and implementation of alternatives to conventional hospitalisation have been developed in recent years [10–16]. Shortstay units, respiratory day hospitals and home-based programmes, such as home hospitalisation, are good examples of

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### Support statement

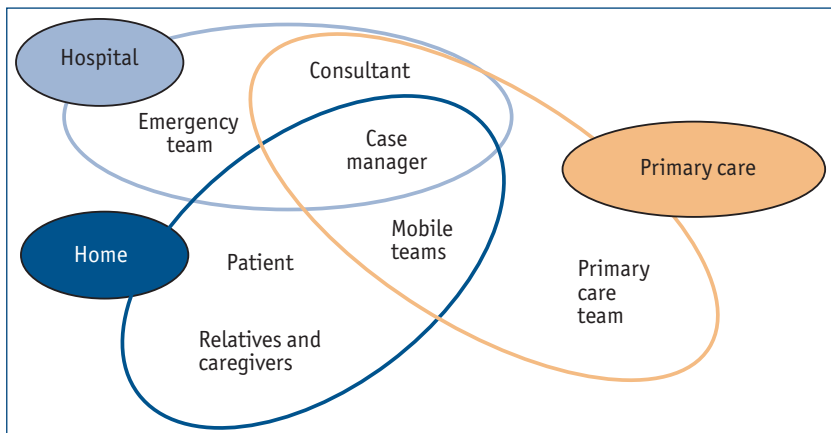
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**Figure 1**  
Evolving trends of healthcare to support integrated care services. Shared-care arrangements among levels of care are required to apply patient-oriented clinical guidelines.

innovative services addressing COPD patients. Integrated care interventions bridging the gap between primary care and respiratory specialists with the support of (ICT) have been shown to be effective in preventing unplanned hospitalisations in COPD patients [17]. Ongoing small-scale pilot experiences in Europe, such as the European Union-funded Better Breathing project [18], are exploring the potential of integrated care services to address care pathways that cover the whole spectrum of COPD, from early diagnosis to end-stage disease, including end-of-life support.

It should be noted, however, that a holistic approach to integrated care in chronic patients needs to look beyond prevention and/or management of crises. Instead, the principal targets should be early diagnosis and prevention together with future personalised care strategies launched at early stages of COPD and aiming at modulation of disease progress and enhancement of prognosis. Successful strategies to address these challenges entail a progressive phasing-out of the classical disease management approach in favour of patient-oriented strategies,

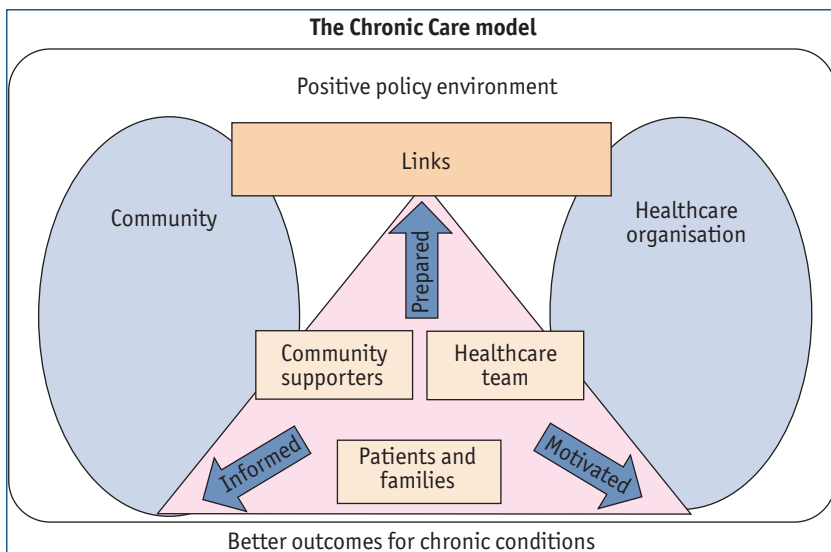
including the adoption of a new health paradigm fitting the needs of chronic care.

## The need for a holistic approach

The ageing of the population and changes in lifestyle are central factors in the increasing prevalence of chronic disorders, which is expected to continue over the coming decades, causing further dysfunction in healthcare systems worldwide [19-23]. Chronic noncommunicable diseases represent almost 80% of the burden on healthcare systems in Europe [24], playing a dominant role in both mortality and disabilities. The urgent need for substantial change in the delivery of care for chronic patients, as well as better integration with social support services, is widely accepted. In 2002, the World Health Organization (WHO) launched the Innovative Care for Chronic Conditions (ICCC) initiative, formulating basic principles and strategies to improve the management of chronic patients.

Briefly, changes in lifestyle aiming at disease prevention and the promotion of wellbeing, empowerment of patients and relatives in disease management and "share care" arrangements (figure 1), are all necessary elements to improve the efficiency of chronic care. There is no doubt that fragmentation within and between healthcare [25] and community services is a major limiting factor for a practical adoption of the principles formulated in the Chronic Care model (figure 2). Moreover, management of comorbidity is a major challenge often overlooked by evidence-based diagnosis and treatment using disease-specific clinical guidelines [26].

**Figure 2**  
Diagram of the integrated care model proposed by the WHO's ICCC initiative. As represented in the figure, interplay between the roles of patients/carers, healthcare/public health and community services is needed. (See [19-22] for further explanations).



## The challenges of deployment

Several disease-specific randomised controlled trials (RCTs) undertaken in patients with chronic heart failure [27, 28], COPD [9-17], diabetes [29, 30] and other conditions have consistently shown the potential of integrated care to enhance clinical outcomes while containing costs.

Integrated care programmes have traditionally focused on rather advanced disease conditions, tackling home hospitalisation of patients who would otherwise require conventional hospi-

talisation. Strategies for prevention of unplanned hospitalisations have also been successfully explored [10, 17], but they may not be financially sustainable in the long term. A common problem in all these pilot studies is that disease-specific trials have shown high internal validity, but a questionable external validity because of their high exclusion rates [17], mainly due to severe comorbid conditions (~60% exclusion of cases). These could potentially be managed through wider programmes addressed to frail patients with multiple severe chronic disorders.

The second most important exclusion factor, often present in frail patients, is a lack of appropriate social support. As suggested previously, the current focus on advanced chronic conditions needs to be shifted toward the development of preventive integrated care strategies, addressed to people in the early stages of (or even at high risk of developing) chronic disorders. The ultimate aim should not be solely to manage disease, but to improve the prognosis of chronic disorders. For this, highly standardised interventions together with continuous evaluation of results will be required.

In order to face all these challenges, more attention is being paid to the evolution of health systems from a provider-centred perspective to a patient-focused approach. This is an essential development if the epidemiological changes associated with population ageing and the growing prevalence of chronic disorders are to be addressed successfully [30]. Significant changes in healthcare organisation and education are urgently needed in order to prepare healthcare professionals for new and evolving roles.

In this new scenario, a major issue will be the extensive use of ICT as a tool for the public to access the system in new ways, and as a medium to effectively promote information sharing among professionals, the public and formal and informal caregivers. While the role of ICT in supporting innovative integrated care services is unquestionable, there are several unsolved issues. Any platform must be modular to enable expansion and robust through redundancy. Co-development and interoperability of ICT platforms are major technological elements contributing to sustainability.

These technological challenges must be overcome to achieve standardisation and ensure shared arrangements across levels of care. The final aim is primarily concerned with normalising service delivery practices and integrating them seamlessly with ICT. The above elements must go hand in hand with the necessary financial rear-

rangements, supported by well-defined business cases [32–39]. The rationale is that the interplay among these factors will favour the implementation of new systems in daily practice, leading to growth in provision and uptake.

The transitional phase from existing pilot experiences to extensive deployment of health and social services targeting selected groups entails a choice of which target services should be validated. They are selected on the basis of the knowledge and experience acquired through small-scale controlled pilot studies showing positive outcomes in terms of efficiency, user satisfaction and overall cost savings [9, 17], and they cover a broad spectrum of health problems, from those affecting citizens at risk or in the early stages of disease to those characterising patients with advanced chronic disorders. It is important to note that there are significant gaps in the methodology of validating innovative healthcare services supported by ICT. These partly explain the lack of data formally validating the role of ICT in healthcare. The current approach is to use RCTs, although health technology assessment agencies and experts acknowledge the need for new and more appropriate methodological approaches conceived specifically for validating healthcare services and their associated ICT tools.

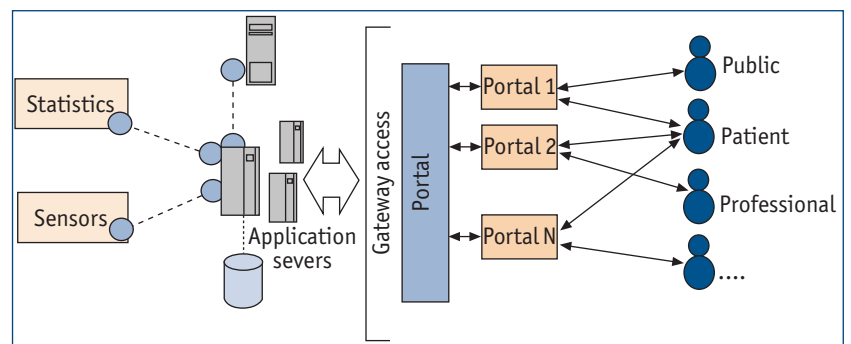
## The NEXES project

NEXES is the short name of the project "Supporting Healthier and Independent Living for Chronic Patients and Elderly" (European Union Competitiveness and Innovation Programme grant 225025), which will run from 2008 to 2011. The project addresses the transitional phase from existing pilot experiences to the deployment of health and social services targeting selected groups of patients. It supplements and/or represents an alternative to existing conventional approaches.

NEXES fits into European policies aiming at

**Figure 3**

*The four integrated care services described in the text will be developed in the three sites. Interoperability among sites will be explored through collaboration with the large-scale pilot study (SOS).*



adapting regional healthcare services to face new demographic and lifestyle challenges and the increased prevalence of chronic illnesses. It will run in Spain, Norway and Greece (figure 3) in close relationships with a large European project (SOS) that includes 12 countries, aiming at cross-country interoperability of electronic prescriptions and patient summary reports. NEXES will also look for strong interactions with other regional deployment studies.

The main objective is to evaluate the potential for generalisation of four specific services targeting people at risk and patients with chronic illnesses. NEXES will mainly address patients with one or more of COPD, chronic heart failure and type II diabetes.

The central hypotheses of the project are that integrated care based on standardised pathways supported by ICT may enhance clinical outcomes and generate satisfaction for patients, carers and health professionals. It may contain costs by preventing duplication. Moreover, it may have a positive impact on disease progress and prognosis. Should all (or some) of these outcomes happen, the sustainability of the healthcare model promoted by NEXES will be ensured.

The project outlines the need to consider three pivotal aspects for a successful deployment: organisational issues, including workflow redesign and redefinition of the roles of the public and professionals; the legal and ethical implications associated with these changes; and the educational needs of professionals and the public.

NEXES will tackle a range of challenges posed by changing healthcare needs.

- Sharing between different levels of healthcare (primary care being central) and reformulating the role of nurses as case managers.
- Strengthening the active role of the public in disease prevention and management.
- Developing treatment strategies centred on the patient, which facilitate the

management of comorbidities.

- Improving communication between healthcare services and community support services.
- Stratifying needs and personalising healthcare.
- Developing new accessibility and communication methods between patients and the healthcare system.

In this scenario, ICT plays a fundamental support role. At the same time, there are significant technological requirements.

- ICT platforms must be modular and interoperable.
- There must be support for sharing information and decisions among healthcare levels and community services, and with patients and carers.
- Specific and/or continued remote monitoring of selected patients must be available.
- Support tools must be provided for managing clinical knowledge, prediction and personalisation of the healthcare service.

Services will be validated through large-scale RCTs including more than 5,000 patients. The services have been selected on the basis of small-scale controlled pilot studies as detailed earlier in this article. The first three services described in Box 1 address important aspects related to chronic patients. The target groups for these services will be patients with heart failure, type II diabetes and COPD. The fourth service (Support) will encompass a variety of heterogeneous niches wherein ICT has a clear potential to play a relevant role enhancing home-based healthcare delivery.

All services will be assessed in three distinct locations (Barcelona, Spain; Central Norway; and Athens, Greece), despite some existing differences in the specifics of healthcare organisation. The impact of heterogeneities among sites will be evaluated. The differences among sites may offer

### Box 1 The four services to be validated by the NEXES study

**Wellness and rehabilitation** promoting healthy lifestyles in clinically stable chronic patients, enhancing their self-management and improving compliance with prescribed pharmacological and nonpharmacological interventions. Among the latter, physical activity and muscle training will be the principal components.

**Enhanced care for frail patients to prevent** unplanned hospitalisations.

**Home hospitalisation of chronic patients with severe exacerbations** aiming at optimisation of home hospitalisation, enhancing interactions with primary care and reducing the rate of readmissions.

**Support** for diagnosis and/or therapeutic procedures including collaborative tools for professionals working at different healthcare levels to enhance their potential for action in home-based interventions.

opportunities to plan cross-border co-developments for the deployment phase.

One of the primary objectives of NEXES is to provide robust results to health technology assessment agencies and decisionmakers in order to facilitate the extensive deployment of the services and the sustainability of the care model (table 1).

## Specifics of the field studies

### 1. Wellness and rehabilitation

Previous studies indicate that standardised care paths in clinically stable COPD patients, using mobile technologies, enhance self-management of the disease and improve clinical outcomes [17, 40]. Moreover, physical activity is proven to enhance prognosis [41–45], but unfortunately the long-term sustainability of the training-induced effects of supervised rehabilitation programmes is an unmet need, due to logistical and cost issues. The main hypotheses behind the study are as follows.

- A standardised wellness and physical rehabilitation programme can be carried out at home using mobile technology and it is organisationally and economically sustainable. Such a programme generates synergies between pharmacological and nonpharmacological therapeutic strategies. Moreover, it brings positive outcomes on behavioural styles and self-management of chronic conditions, clinical indicators, quality of life, acceptability and costs.
- The home-based rehabilitation programme makes it possible to sustain the physiological benefits achieved with supervised muscular training in the long term.
- The characteristics of the programme can be transferred easily to other chronic conditions that benefit from physical training programmes.

The principal aim is to assess the efficacy and sustainability of a low-cost programme supported by wireless technology to enhance self-management of disease in clinical stable COPD and cardiac patients. A secondary aim is to demonstrate the efficacy of home-based physical rehabilitation to maintain the physiological effects of supervised skeletal muscle training in the long term.

The study is designed as a two-phase trial. In Phase I, we are planning to examine 200 COPD patients (80 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II, 80 GOLD III and 40 GOLD IV) before and after an 8-week supervised endurance training programme. After training, the patients will be ran-

**Table 1** NEXES evaluation strategy

1	Assessment of clinical effectiveness of four services through large field studies
2	Evaluation of associated costs (direct and indirect) for each type of service
3	Analysis of factors influencing extensive deployment of the services. Proposal of strategies for adoption. Analysis of associated business models
4	Analysis of cross-country issues relevant to the transfer of information/knowledge among the three sites
5	Identification of leading teams across Europe willing to share NEXES experience and stimulation of synergies with other platforms

domised (1:1 ratio) to the intervention arm with mobile technologies or a control arm with conventional care. The two groups will be followed up for 18 months. Phase II of the study will have a similar design and purposes, but will include 500 patients with COPD and/or heart failure and have a shorter (4-week) supervised training period.

The ICT platform will include mobile phones with questionnaires, messaging and wireless sensors (pulse oximetry and physical activity), a call centre and a web-based application for professionals and patients/carers, including telecollaboration tools. Target variables and expected results are: 1) improved health status; 2) long-term sustainability of training-induced physiological effects of skeletal muscle training; 3) increased adherence to treatment; 4) improved lifestyle; and 5) reduction in healthcare expenses.

### 2. Enhanced care for frail patients

In 2006, we reported that a standardised low-intensity integrated care intervention, with the support of a web-based call centre and a portable system used by specialised nurses during home visits, prevented hospitalisations in COPD patients who were included in the study immediately after hospital discharge and followed up for 12 months [17]. Shared care agreements with primary care teams were a key element in the success of the intervention. The study showed significant cost savings and satisfaction of patients and professionals involved.

A similar study in COPD patients at high risk of unplanned hospitalisation was carried out during 2006 [40]. The study showed the potential of wireless systems for patient self-monitoring at home, as well as the beneficial impact of integrated care to reduce emergency room visits, increase planned hospitalisations and reduce mortality. Current data on the impact of chronic conditions in tertiary care hospitals suggests that enhanced care services for frail patients are needed promptly. Identified target clusters of dis-

eases were chronic heart failure, COPD and diabetes type II.

While the pilot studies were essentially triggered from the hospital side, in NEXES they should be driven at primary care level, with hospital specialists playing a supporting role. A second important aim of the project is to explore whether results obtained in disease-oriented pilots (COPD) can be reproduced in patient-oriented programmes addressing different disease conditions. It is well known that disease-oriented pilots show high internal validity, but limited potential for generalisation.

The study will be an RCT with 1,400 patients, 700 each in the integrated and conventional care arms. The patients will be followed up for 12 months. The integrated care intervention will consist of the following.

- Comprehensive assessment of the patient including severity of main disease, evaluation of comorbid conditions and analysis of social support requirements.
- Educational programme on selfmanagement of the disease administered at discharge.
- Individually tailored care plan following international guidelines shared across the healthcare system.
- Setting up interactions between the primary care team, community services and the specialised team.

The logistics of the interventions will be customised to suit the specifics of the healthcare organisation in each of the three sites. The ICT platform and associated services will comprise: 1) mobile phones including questionnaires and messaging services; 2) wireless sensors for selected patients in the intervention group; 3) call centre; 4) a mobile application (laptop) with wireless sensors for home-visiting professionals; and, 5) a web-based application for professionals and patients/carers with telecollaboration tools. The expected results are: 1) improved health status; 2) a fall in emergency room and unscheduled hospital admissions; 3) decrease in length of stay; 4) increased adherence to treatment; 5) changes in lifestyle; and 6) a reduction of costs.

### 3. Home hospitalisation and early discharge of chronic patients with severe exacerbations

In 2003, we reported that an integrated home-care intervention in selected COPD exacerbations was cost-effective [9, 11, 37]. Home hospitalisation generated better outcomes at a lower cost than conventional care. We concluded that home-based services should not be seen in opposition to in-patient hospitalisation. They must be

regarded as part of the continuum of care in chronically ill patients. The study revealed a need for the deployment of this type of intervention as a regular healthcare service for COPD patients who suffer exacerbations, under the frame of a properly designed cost-effectiveness analysis. Since early 2006, a home-hospitalisation programme has been deployed in several acute and chronic conditions, showing that with proper re-engineering of the system this type of programme is effective for patients and increases the number of available beds for other healthcare programmes. In NEXES, home hospitalisation has two main aims: 1) to evaluate the added value of a robust ICT platform in improving interactions with patients/carers and the interplay of the programme with primary care services; and 2) to generalise the home-hospitalisation programme to other centres. This programme is mainly a hospital-driven initiative, but share care agreements with primary care services should be explored in order to increase efficiencies. The hypothesis is that home hospitalisation with robust ICT support will enable the generalisation of a sustainable service.

The study will be an RCT (1:1 ratio) with 2,400 patients. Candidates will be patients with acute episodes of exacerbation of chronic conditions. The types of patients with acute problems requiring emergency room admission who showed acceptable clinical outcomes in the Hospital Clínic (Barcelona) programme during 2006–2007 will also be considered for inclusion in the project. Current inclusion criteria are: 1) emergency room admission or hospitalisation for <48 hours; 2) carer available 24 hours per day; 3) ability to understand the programme; and 4) signed consent form. Exclusion criteria are: 1) presence of major comorbid conditions such as advanced cancer, stroke, *etc.*; and 2) living in a nursing home. The intervention group will receive the following.

- Comprehensive assessment, including severity of main disease, evaluation of comorbid conditions and analysis of requirements in terms of social support.
- Educational programme on selfmanagement of the disease administered at discharge.
- Individually tailored care plan following international guidelines.
- Logistics for home support including enabling ICT tools.
- Access to the system during the follow-up period through an ICT platform including a web-based call centre.

The technological platform and support serv-

ices will include mobile phone with questionnaires and messaging, along with wireless sensors for remote monitoring in selected patients. A call centre and mobile application (laptop) with wireless sensors will be provided for home-visiting professionals. Moreover, a web-based application including telecollaboration tools will be available to professionals and patients/carers.

The expected results are: 1) a reduction in hospitalisations and readmissions; 2) a decrease in mortality rate; 3) satisfaction; and 4) cost containment. We expect that it will be possible to expand the inclusion criteria, optimise the burden on the professionals and decrease the impact of these patients on primary care.

#### 4. Support

The programme will provide support for diagnosis and/or therapeutic procedures including collaborative tools for professionals working at different healthcare levels to enhance their potential for action in home-based interventions. The main goal of the programme is to expand the potential of primary care professionals by facilitating the use of diagnostic and therapeutic technologies, with potential remote support (mostly offline) from specialists. A recent study carried out with 4,500 patients in Spain showing the usefulness of a simple web-based application to enhance the quality of forced spirometry in primary care [46] is one example of such activity. The potential to transfer decision-making capabilities to primary care and patient's home is spectacular. It holds out the prospect of new ways of interaction between all levels of healthcare, including patients/carers. No doubt the role of specialists will change for good.

This specific study encompasses a heterogeneous group of services, covering potential applications of the available ICT platform to remotely support different health services. It comprises:

- Remote control of tertiary care programmes (arrhythmias, pulmonary hypertension, minimally invasive systems, etc.) whose deployment is currently limited because of a lack of proper organisational integration.
- Support for specific monitoring between hospital and home. This could be valid for major ambulatory surgery or highly sophisticated home programmes (bone-marrow transplantation).

For obvious reasons, it is difficult to address the methodological issues involved in this programme and the specificities of the evaluation. It is clear that services, not technology, will be

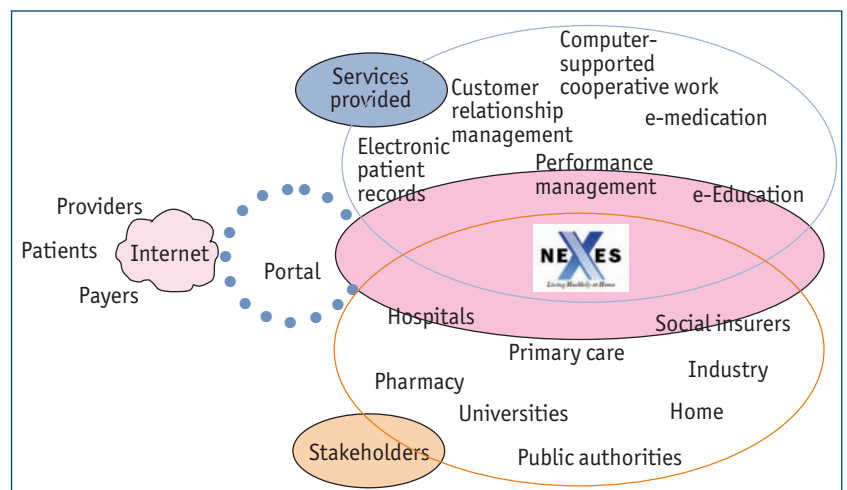
evaluated. It has to be assumed that the technology is proven and robust. Up to 700 cases have been targeted for this study, but the project will include more patients than this. The technological requirements will be as already described for the other three services.

### Potential of the project and functionality of the ICT platform

NEXES is an ambitious project that, together with validation of the four services alluded to previously, will develop strategies for the extensive deployment and sustainability of integrated care pathways for chronic patients. During the lifetime of the project, it is calculated that the NEXES will provide coverage to ~1.5 million people in Catalonia (Spain) – slightly above 20% of the population. The new activities introduced to support integrated care services should generate marked changes in the roles of both citizens and professionals involved.

The abilities of the ICT platform should not be seen as service specific (figure 4). Rather, the platform provides different possibilities to ensure that the activities of patients and professionals take place in the context of predefined patterns of care. Thus, a single functionality can be implemented in different ways, both organisationally or technologically. An example could be "monitoring", which can be performed through a questionnaire by phone call (call centre technology and a nurse asking the questions and recording the answers) or using a mobile phone/PDA (the patient reports directly, the nurse reads answers online). Thus, different services will use different aspects of the platform. Box 2 illustrates the main system functionalities, along with specifics for each of the four integrated care services.

Figure 4  
NEXES services provision model.





**Box 2 System functionalities**

**Patient empowerment functionalities** These aim to allow the patient to be more proactive in the management of his/her conditions and to increase adherence to treatment. It features educational material and strategy to deliver it.

Examples:

- Text-messaging system to promote treatment compliance or warnings*
- Streamed video to promote exercise and weight control*
- Personal diary to keep track of progress*

**Patient selfmonitoring functionalities** These functionalities characterise monitoring in terms of its type, the resources needed (sensors, questionnaires, etc.), scheduling, display features for the patients, etc.

Example:

*Short questionnaire to assess symptoms, administered periodically, either scheduled or nonscheduled, via a mobile phone. An evolving graph for the main variables is presented to the patient and a more complex one to the professional*

**Patient-professional communication functionalities** These include the main features of the equipment used and how it should be invoked or customised to the pattern of care.

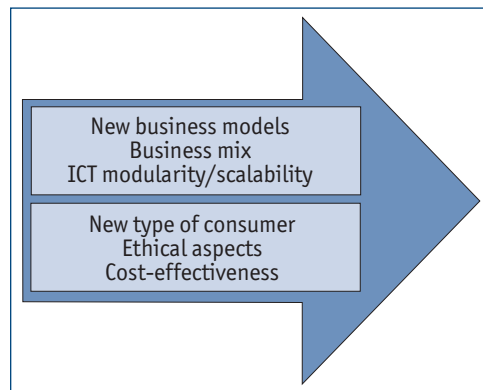
Example:

*A patient could access the control centre in three different ways: phone call via call centre; SMS alarm triggered from mobile phone; via the portal application.*

**Professional-professional communication functionalities** The different capabilities for professional collaboration are included in this group.

Examples:

- Virtual boards*
- E-mail*
- Shared agendas*
- Video conference*



**Figure 5**  
Dimensions of long-term viability in NEXES are seen as the confluence of a set of six basic elements depicted in the figure. It also aims at representing some differences according to their importance and contribution to viability. The bottom block includes three dimensions that are seen as sine qua non for sustained maintenance of the services of NEXES. It includes cost-effectiveness, ethical aspects and the emergence of a new type of consumer.

## Beyond the deployment initiatives

Hopefully, successful deployment of initiatives such as NEXES (figure 4) will lead to sustainable integrated care services for chronic patients (figure 5). Such initiatives should generate mature end-users, both patients and professionals, and ultimately more efficient healthcare delivery.

In the future, it is likely that the implementation of integrated care will generate a need for stratification of chronic patients according to severity and prognosis. In the medium term (5–10 years), preventive and therapeutic clinical interventions are likely to be tailored according to the

disease phenotype and its associated prognosis. For example, a COPD patient with mild-to-moderate disease whose data suggest slow disease progress with no systemic effects may be advised to follow a care path involving a high degree of self-management with low impact on the healthcare system. In contrast, a patient with features indicating rapid progress of lung disease and future development of systemic effects will be monitored closely with a view to relatively high intensity interventions at early COPD stages in order to modulate the disease progress.

In this scenario, we can envisage an optimistic view of COPD. Management of crises (exacerbations) will no longer be the central clinical problem of the disease and COPD will essentially be managed outside the hospital. Moreover, early interventions based on a deep knowledge of the underlying mechanisms of the disease will facilitate modulation of disease progress, with marked positive effects on prognosis.

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