UNIVERSITY OF BEIRA INTERIOR
Engineering

Information Technologies for Pain Management

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Dedicatory

To the memory of my 8-year-old daughter, Carolina,
whose determination, happiness and love inspired me.

" For it was not into my ear you whispered,
but into my heart.
It was not my lips you kissed,
but my soul"

Judy Garland

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"If you want to go fast, walk alone. If you want to go far, walk together"

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"Science, my lad, is made up of mistakes,
but they are mistakes which it is useful to make,
because they lead little by little to the truth"

Jules Verne

Foreword

This thesis describes the research work performed in the scope of the 5-year doctoral research programme and presents its conclusions and contributions. The research activities, were accomplished with the collaboration of several entities such as: the Portuguese telecommunications service provider *PT Comunicações/SAPO*, University of Beira Interior and Hospital Sousa Martins. The research work was supervised by Professor Pedro Araújo, from Department of Informatics, University of Beira Interior, and co-supervised by Professor Joaquim Viana, from Faculty of Health Sciences, University of Beira Interior. This study had no financial support.

This work has been guided from the beginning to ensure its practical applicability and become useful in real-life. Always sought to demystify the idea that science is restricted to laboratories and with merely academic scope. Thus, in this work we have tried to contribute to the advancement of knowledge in terms of computer science as well as to provide oriented solutions to patients and health care professionals (HCP). This practical and pragmatic approach allowed not only the validation of methodologies and techniques but also contributed to increase the responsibility and accuracy involved in the research.

On the one hand, a part of the monitoring system was developed in cooperation with *PT Comunicações/SAPO* in terms of web-based forms and web services that enable the ubiquitous monitoring of pain combined with a Personal Health Record (PHR), called *Meu Sapo Saúde*. On the other hand, the mathematical models that comprise the computerised clinical decision support system were developed in laboratory, whereas its validity was tested during a randomised controlled trial (RCT) carried in the Hospital Sousa Martins, located in the city of Guarda, Portugal.

The research work developed during the doctoral programme and described in this thesis is the consequence of the activities performed in three distinct environments: enterprise, academia and hospital. These different perspectives provided an unique and fruitful experience with permanent challenges that enhanced my research skills and capabilities, that gave origin to additional research topics, to produce a patent (submitted to *Instituto Nacional de Propriedade Industrial*), and to publish in international journals. All publications were prepared following a strategy of complementarity so as to improve the know-how and experience in the accomplishment of the following topics: systematic review, meta-analysis, RCT, book chapter, paper on conference, and working paper. In addition, the research work was conducted according several standards and guidelines, namely: PRISMA statement [1,2], Cochrane Collaboration's tools [3], CONSORT statement [4] and IMMPACT recommendations [5,6].

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[6] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.

List of Publications

Articles included in the thesis resulting from this doctoral research programme

1. **Best Paper Award: Contribution of Web Services to Improve Pain Diaries Experience**
Nuno Pombo, Pedro Araújo, Joaquim Viana, Benjamin Junior, and Rita Serrano (2012). Lecture Notes in Engineering and Computer Science: Proceedings of The International MultiConference of Engineers and Computer Scientists 2012, IMECS 2012, 14-16 March, Hong Kong, vol. 1, 2012, pp589-592.

2. **Book Chapter: Web Services for Chronic Pain Monitoring**
Nuno Pombo, Pedro Araújo, and Joaquim Viana (2012). IAENG Transactions on Electrical Engineering Volume 1: Special Issue of the International MultiConference of Engineers and Computer Scientists, 2012. Sio-Iong Ao, Alan Hoi-shou Chan, Hideki Katagiri and Li Xu, Eds. World Scientific Publishing Company, 2012, pp148-160.

3. **Applied Computer Technologies in Clinical Decision Support Systems for Pain Management: A Systematic Review**
Nuno Pombo, Pedro Araújo, and Joaquim Viana (2013)
Journal of Intelligent & Fuzzy Systems (IOS Press), accepted for publication, 2013.

4. **Mobile and Web-based Systems for Chronic Pain Monitoring: A Systematic Review and Meta-analysis**
Nuno Pombo, Kouamana Bousson, Pedro Araújo, and Joaquim Viana (2013), Revised version re-submitted for publication in an ISI-indexed international journal, 2013.

5. **Interdisciplinary Concept Transfer from Aerospace Sciences to Medical Decision-making Based on Multisensor Data Fusion**
Nuno Pombo, Kouamana Bousson, Pedro Araújo, and Joaquim Viana (2013)
Informatics for Health and Social Care, accepted for publication, 2013.

6. **Evaluation of a Ubiquitous and Interoperable Computerised System for Remote Monitoring of Ambulatory Post-operative Pain: A Randomised Controlled Trial**

Nuno Pombo, Pedro Araújo, Joaquim Viana, and Manuel Dias da Costa (2013)

Technology and Health Care (IOS Press), accepted for publication, 2013.

7. **Design and Evaluation of a Decision Support System for Pain Management Based on Data Imputation and Statistical Models**

Nuno Pombo, Paulo Rebelo, Pedro Araújo, and Joaquim Viana (2013), Submitted for publication in an ISI-indexed international journal, 2013.

Other publications resulting from this doctoral research programme not included in the thesis

8. **Knowledge Discovery in Clinical Decision Support Systems for Pain Management: A Systematic Review**

Nuno Pombo, Pedro Araújo, and Joaquim Viana (2013)

Artificial Intelligence in Medicine (Elsevier), accepted for publication, 2013.

9. **Evaluation of a Smartphone Application connected to a Web-based System for Remote Monitoring of Post-Operative Pain in Ambulatory Surgery: a randomised controlled trial**

Joaquim Viana, Nuno Pombo, Pedro Araújo, and Manuel Dias da Costa (2013), Submitted for presentation on the Euroanaesthesia 2014.

Resumo

Milhões de pessoas em todo o mundo sofrem de dor, aguda ou crónica o que desperta o interesse da sua deteção, avaliação e tratamento. A importância da dor é evidenciada pelo facto de ser considerada o quinto sinal vital conjuntamente com a pressão arterial, temperatura, frequência cardíaca e frequência respiratória. Contudo, ao invés destes quatro parâmetros fisiológicos a dor não pode ser representada de forma objetiva, pois reflete um estado emocional que ocorre na mente de cada individuo, pelo que podemos dizer em rigor que a "estimamos" ou "traduzimos" ao invés de a medir. Por este motivo, o autodiagnóstico é considerado o método mais fiável de avaliação da dor, em que os pacientes são periodicamente solicitados a indicar a intensidade e os sintomas relacionados com a mesma. Assim, nos últimos anos verificou-se um aumento da utilização de sistemas computorizados baseados em dispositivos móveis e tecnologias Internet, designados por diários eletrónicos de dor, possibilitando aos pacientes a comunicação da sua dor. Devido ao facto destes sistemas serem essencialmente utilizados através de dispositivos móveis e da Internet deu origem a um novo paradigma de acompanhamento médico não apenas baseado em visitas clínicas presenciais mas igualmente em contactos, através da interação com o sistema de forma ubíqua, em qualquer local e a qualquer momento. No entanto, muitos destes sistemas foram desenhados para interagir diretamente com o paciente sem a supervisão de um profissional de saúde e/ou sem evidências de confiabilidade ou precisão. Além disso, a análise das soluções existentes revelou a falta de integração entre sistemas, escassez de formulários online e reduzida interação entre pacientes e profissionais de saúde em termos de obtenção e consulta de informação. Inclusive, a fiabilidade e precisão dos sistemas computorizados para gestão da dor raramente é demonstrada e os estudos sobre os efeitos da tecnologia sobre pacientes e profissionais de saúde permanecem escassos.

Esta tese é focada nos desafios decorrentes da aplicação de tecnologias de informação na gestão da dor e tem como objetivo propor um sistema que inclua interfaces especificamente orientadas a pacientes e profissionais de saúde, através da utilização de dispositivos móveis e Internet. Desta forma pretende-se apoiar a tomada de decisão médica através da disponibilização de informação resultante da análise dos dados recolhidos pelo sistema. Tendo em conta os conceitos de *cloud computing* e interoperabilidade, são usados *web services* e um registo eletrónico de saúde (PHR) de forma a efetuar-se a gestão de dados e o respetivo armazenamento.

Um ensaio clinico randomizado foi implementado para se determinar a eficácia do sistema de monitorização proposto. O estudo decorreu durante seis semanas e evidenciou as vantagens proporcionadas pelo acesso ubíquo a profissionais de saúde e pacientes, permitindo a sua

interação com o sistema a qualquer momento e em qualquer lugar através do uso de *web services* para envio e receção de dados. Para além disso, os dados obtidos foram armazenados num registo eletrónico de saúde garantindo-se assim integridade, segurança e facilidade de acesso a pacientes e profissionais de saúde. O estudo evidenciou que a maioria dos participantes recomendam o sistema ao mesmo tempo que reconhecem a sua adequação para a gestão da dor sem a necessidade de conhecimentos avançados em novas tecnologias. Além disso, o sistema permitiu a definição e a gestão de tratamentos orientados aos pacientes com reduzido tempo de intervenção do profissional de saúde. Foi evidenciado que o acompanhamento dos pacientes por parte dos profissionais de saúde na fase inicial da monitorização é determinante para a satisfação dos pacientes, influenciado a opinião relativamente à recomendação e utilidade do sistema na melhoria da gestão da dor. Não se verificaram diferenças significativas entre o grupo de intervenção e o grupo de controlo, respeitante à qualidade dos tratamentos prestados.

Com base nos dados recolhidos durante o ensaio clínico, foi desenvolvido um sistema de apoio à decisão clínica que permite a emissão de alertas, relatórios e monitorização orientada ao protocolo de tratamento de cada paciente. Este sistema é baseado na imputação de dados em combinação com modelos estatísticos (*one-way ANOVA*, *Kruskal-Wallis* e *Tukey-Kramer*) e é designado por: *Patient Oriented Method of Pain Evaluation System* (POMPES). O sistema mostrou-se preciso relativamente às decisões geradas comparativamente às indicações prestadas pelo profissional de saúde, revelando-se assim adequado para a gestão da dor. A aptidão do sistema para atribuir valores aos dados não preenchidos pelo paciente e a capacidade de deteção de estabilidade e/ou alterações nos sintomas de dor são características determinantes para a precisão do sistema.

Por fim, foi proposto um método para determinar o efeito de sistemas computorizados nas diferentes dimensões da dor, inspirado na capacidade dos sistemas aeroespaciais para lidar com múltiplas fontes de dados que por sua vez podem apresentar diferentes complexidades e precisões. Este modelo resulta da combinação da análise quantitativa decorrente da fusão de dados com um modelo qualitativo baseado na comparação do desvio padrão com os valores das expectativas matemáticas. O modelo foi aplicado em diversas dimensões da dor, tendo permitido observar que os registos eletrónicos e os registos em papel apresentam resultados equivalentes nos seguintes tópicos: ansiedade, depressão, interferência e intensidade da dor. Pelo contrário, os registos eletrónicos superaram os registos em papel em termos de catastrofização e incapacidade originada pela ocorrência de dor. Este método revelou ser adequado, inteligível, simples de implementar e a sua generalização permite avaliar o efeito de sistemas computorizados comparativamente com outras abordagens independentemente do contexto ou área de investigação e atividade.

Apesar de promissoras, estas conclusões apresentam diversas oportunidades, nomeadamente novos estudos devem ser realizados com o objetivo de se avaliar os custos decorrentes da

aplicação do sistema proposto não apenas para os pacientes mas igualmente para o sistema nacional de saúde (SNS). A contribuição na melhoria da adesão dos pacientes às terapêuticas ministradas e a eficácia dos tratamentos são aspetos que poderão ser aprofundados através da realização de ensaios clínicos adicionais. Por fim, está prevista a realização de um ensaio clínico complementar envolvendo pacientes com dor crónica, tendo como objetivo a validação do sistema de apoio à decisão clínica proposto quando aplicado à monitorização durante um período de tempo alargado.

Palavras-chave

Dor: gestão, avaliação, monitorização. Sistemas de apoio à decisão clínica.
Computação: mHealth, ubiquidade, cloud computing, data fusion, data imputation. Web services. Registos eletrónicos de saúde (PHR).

Resumo Alargado

Introdução

Esta secção resume, em Língua Portuguesa, o trabalho de investigação descrito na tese de doutoramento intitulada "Information Technologies for Pain Management". A parte inicial desta secção descreve o enquadramento da tese, define o problema abordado e os objetivos do doutoramento, apresenta ainda o argumento e as principais contribuições da tese. A secção termina com a apresentação resumida das principais conclusões e indicação de diversas perspetivas de investigação futura.

Enquadramento da Tese

De acordo com a associação internacional para o estudo da dor (IASP) [1,2], a dor é uma experiência sensorial e emocional desagradável, relacionada com lesão tecidual real ou potencial, ou descrita em termos de tal lesão. Apesar de ser um sintoma e uma das causas mais frequentes da procura de auxílio médico continua a ser pouco estudada e percebida [3]. A sua importância é evidenciada pelo facto de ser considerada o quinto sinal vital [4,5] conjuntamente com a pressão arterial, temperatura, frequência cardíaca e frequência respiratória. Contudo, ao invés destes quatro parâmetros fisiológicos a dor não pode ser representada de forma objetiva, pois reflete um estado emocional que ocorre na mente de cada individuo, pelo que podemos dizer em rigor que a "estimamos" ou "traduzimos" ao invés de a medir. Além do mais, a dor manifesta-se das mais variadas maneiras e provoca diferentes experimentações de acordo com a sua duração. Quando ocorre com uma duração relativamente curta é denominada por dor aguda. Ao invés, quando persiste durante um período de tempo prolongado, geralmente igual ou superior a três meses, é considerada dor crónica [6]. Em ambas as situações a dor é uma experiência individual representando uma sensação percetiva e subjetiva [7], que envolve fatores fisiológicos, neurológicos e psicológicos. Deste modo podemos considerar que a dor não é um elemento isolado mas sim uma experiência multidimensional [8–12], que compreende aspetos sensoriais (ex: localização, intensidade), afetivos (ex: depressão, ansiedade) e cognitivos (ex: qualidade de vida).

A ocorrência de dor envolve anualmente gastos avultados quer em despesa médica [13], quer em custos indiretos resultantes da diminuição da qualidade de vida das pessoas e da redução de produtividade laboral [14–16]. Além disso, quando se verifica dor crónica os custos da sua

terapêutica tendem a ser amplamente dispendiosos devido à necessidade de realização de inúmeros tratamentos por um período de tempo alargado [17]. Isto significa, que a monitorização da dor pode ocorrer em ambiente clínico ou em regime ambulatório no domicilio do paciente tornando assim relevante a correta avaliação da dor, tanto mais que esta é muitas vezes subestimada pelos profissionais de saúde impedindo que o tratamento seja realizado da forma mais conveniente [18–20]. A importância da gestão da dor é atestada pelas normas sugeridas por exemplo pela *Joint Commission on Accreditation of Healthcare Organizations* [21], que refere explicitamente a necessidade de avaliação e registo da dor para cada paciente. Devido ao facto do autodiagnóstico ser considerado a forma mais precisa de avaliação da dor [22,23], os pacientes são periodicamente solicitados a indicar a intensidade e os sintomas relacionados com a dor. Estes registos são depois utilizados para os mais diversos fins, tais como: triagem, diagnóstico, tratamento e monitorização da dor.

Os sistemas computorizados que permitem o registo de valores de dor são denominados por diários eletrónicos de dor e constituem geralmente o principal meio de recolha de dados durante o processo de monitorização. Desejavelmente os dados recolhidos destes sistemas deverão ser usados posteriormente de forma organizada e inteligível com o objetivo de gerarem informação útil que permita apoiar os profissionais de saúde na tomada de decisão médica. Nos últimos anos os diários eletrónicos de dor não apenas substituíram as metodologias tradicionais de registo baseadas em papel, como permitiram aumentar a experiência decorrente da sua utilização através da disponibilização de informação médica, solicitação de inserção de dados através de alarmes, emissão de respostas automáticas e ainda controlo de doenças [24]. O facto destes sistemas serem essencialmente utilizados através de dispositivos móveis e da Internet deu origem a um novo paradigma de acompanhamento médico baseado em contactos e não apenas em visitas clínicas presenciais [25]. Por um lado, a possibilidade de se interagir com o sistema de forma ubíqua, em qualquer local e a qualquer momento oferece inúmeras oportunidades para a prestação de cuidados de saúde. Por outro lado, o desenvolvimento tecnológico dos dispositivos móveis registou avanços significativos ao nível da capacidade de armazenamento e autonomia [26] para além do aumento da capacidade de acesso a recursos online [27] o que contribuiu para o aumento da aplicação destes dispositivos na medicina. A crescente utilização dos diários eletrónicos de dor tem possibilitado o registo de dor não apenas no momento em que ocorre, mas igualmente em termos de retrospetiva para um determinado período temporal.

Contudo, a introdução de tecnologia na triagem, diagnóstico, tratamento ou monitorização de pacientes com ocorrência de dor levanta diversos desafios. Primeiro, o modo como os diferentes perfis de utilizadores, tais como pacientes e profissionais de saúde, devem interagir com o sistema. Segundo, de que modo os dados devem ser recolhidos, armazenados e disponibilizados. Terceiro, de que modo se deve parametrizar, analisar e produzir decisões baseadas nos dados obtidos. Quarto, de que modo informar os pacientes e os profissionais de

saúde acerca das decisões tomadas. Por fim, de que modo determinar o efeito causado pelo uso de tecnologia.

O âmbito desta tese é limitado a sistemas computorizados que permitam o apoio à tomada de decisão clínica ou diários eletrónicos de dor, que incluam dados sobre avaliação da dor, aguda ou crónica, ou que alternativamente produzam resultados baseados na ocorrência de dor em pelo menos uma das seguintes atividades: triagem, diagnóstico, tratamento ou monitorização. O trabalho de investigação apresentado nesta tese é focado nos desafios decorrentes da aplicação de tecnologias de informação na gestão da dor, mais concretamente com a proposta de um sistema que permita a integração dos diários eletrónicos de dor com os sistemas de apoio à decisão clínica. A metodologia desta integração é baseada nos conceitos de ubiquidade, interoperabilidade e decisões baseadas em conhecimento, de forma que a sua combinação resulte num sistema de monitorização remoto. Primeiro, a ubiquidade é verificada através do desenvolvimento de um software (app) orientado à utilização em dispositivos móveis e que usa uma ligação à Internet para enviar e receber dados. Segundo, o uso do registo eletrónico de saúde (PHR) e de *web services* garantem a interoperabilidade requerida pelo sistema. Finalmente, a decisão baseada em conhecimento é suportada por modelos matemáticos implementados no módulo de apoio à decisão que é integrante do sistema de monitorização e ainda na metodologia proposta de avaliação do efeito dos sistemas computorizados nas diferentes dimensões da dor.

Descrição do Problema e Objetivos da Investigação

O problema abordado nesta tese de doutoramento é o autodiagnóstico da dor pelos pacientes utilizando um sistema de informação que garanta a obtenção de uma avaliação precisa e que consequentemente contribua para a melhoria das terapêuticas ministradas pelos profissionais de saúde. Motivado pelo impacto das tecnologias de informação na gestão da dor, o estudo inicial teve como objetivo caracterizar os sistemas de apoio à decisão clínica e os diários eletrónicos de dor. No inicio deste programa doutoral, a precisão e aplicabilidade dos diários eletrónicos comparativamente ao registo em papel já era uma realidade abordada em diversos estudos [28–36]. No entanto, foram detetadas várias limitações nestes sistemas tais como: a generalidade dos diários eletrónicos são projetados para interagir diretamente com os pacientes sem a supervisão de um profissional de saúde [37,38] e/ou sem evidência de confiabilidade ou precisão. Como já referido anteriormente, a dor é uma experiência multidimensional, logo a sua terapêutica requer acompanhamento de diversos profissionais de saúde em diferentes especialidades, pelo que é desejável que a informação do paciente possa ser obtida e disponibilizada de forma fácil e segura (ex: evitando-se redundância de exames

médicos, rápida obtenção do historial do paciente, e ainda forma segura e permanente de armazenamento dos dados de saúde).

Alguns estudos apresentam soluções integradas através da combinação de diários eletrónicos com PHR ou sistemas de informação hospitalares, contudo a sua aplicação é limitada a meros repositórios de dados [32] ou à utilização restrita em ambiente hospitalar [39,40]. Por outro lado, alguns estudos usam redes de área corporal (BAN) [41], ou integram dispositivos médicos e sensores tais como medidores de atividade [42], eletrocardiografia (ECG) [43,44] ou eletroencefalografia (EEG) [45]. No entanto, o ECG e o EEG requerem supervisão de profissionais de saúde e condições especificas para que possam originar resultados precisos, como por exemplo a imobilidade do paciente, o que limita o seu uso na monitorização remota da dor. Além disso, a conectividade entre software e o hardware, a complexidade da topologia da rede, a implementação, manutenção e custos são limitações adicionais ao uso das BAN na monitorização de pacientes que sofrem com a dor.

Os sistemas de apoio à decisão clínica propostos na literatura apresentam igualmente limitações, nomeadamente em termos de ubiquidade e acessibilidade. Muitos destes sistemas restringem o acesso remoto através de dispositivo móvel e/ou Internet aos profissionais de saúde [46–54], e os que permitem acesso aos pacientes fazem-no de forma limitada em termos de funcionalidades disponibilizadas [55,56]. Por último, a complexidade do contexto médico levanta diversos desafios para o desenho, desenvolvimento e aplicação dos sistemas de apoio à decisão clínica [57], essencialmente devido à dificuldade de modelação de problemas envolvendo um grande número de variáveis. Esta dificuldade resulta geralmente em sistemas pouco precisos devido à *overspecialisation* ou a *overfitting* [58] e consequentemente em diagnósticos incorretos e inadequados [54].

O principal objetivo desta tese é o de apresentar um sistema computorizado para a monitorização da dor que inclua pacientes e profissionais de saúde, ao mesmo tempo que proporciona a integração de dados entre o diário eletrónico de dor e o sistema de apoio à decisão clínica. O sistema terá de ser capaz de monitorizar pacientes independentemente de sofrerem de dor aguda ou crónica, possibilitando a geração de relatórios e alertas em tempo-real, além de fornecer *feedback* direcionado para pacientes e profissionais de saúde. Estas ações devem ser baseadas em modelos matemáticos inteligíveis e ajustáveis. Para além disso, o sistema proposto deverá facultar acesso à informação de forma ubíqua e interoperável a pacientes e profissionais de saúde.

O trabalho de investigação necessário para cumprir o objetivo da tese foi estruturado nos seguintes objetivos secundários:

1. Compreender as soluções existentes relacionadas com as tecnologias de computação usadas pelos sistemas de apoio à decisão clínica aplicados à gestão da dor, descrevendo as diferentes

abordagens e apresentando as suas vantagens e limitações com o intuito de se produzir o estado da arte com especial destaque na identificação dos diferentes métodos de aprendizagem automática e respetiva caracterização em termos de precisão, sintomas, apoio clínico prestado, ubiquidade e acessibilidade da informação.

2. Compreender as soluções existente relacionadas com os sistemas móveis e baseados na Internet para a gestão da dor, descrevendo as diferentes abordagens e apresentado as suas vantagens e limitações com o intuito de se complementar o estado da arte produzido no ponto anterior, destacando-se as metodologias aplicadas na obtenção e transmissão de dados entre os pacientes e os profissionais de saúde.

3. Comprovar a eficácia e a exequibilidade do sistema de monitorização proposto através da realização de um ensaio clínico envolvendo pacientes em regime ambulatório de pós-operatório divididos entre grupo de tratamento que usa o sistema e grupo de controlo.

4. Apresentar um novo método capaz de apoiar as decisões clínicas com base nas condições do paciente e nos dados de autodiagnóstico conjugados com as regras de tratamento e protocolos definidos pelos profissionais de saúde. Este método será suportado por conceitos matemáticos e/ou de aprendizagem automática e deverá ser desenvolvido tendo em conta critérios de precisão, fiabilidade e simplicidade.

Argumento da Tese

Esta tese propõe uma nova abordagem para a monitorização de pacientes que sofrem de dor tendo como base a ubiquidade e interoperabilidade de um sistema de informação. O argumento apresentado nesta tese é o seguinte:

O caracter multidimensional e subjetivo da dor requer uma solução tecnológica que englobe módulos especificamente orientadas para os pacientes e para os profissionais de saúde. Em primeiro lugar, os pacientes devem ser capazes de interagir com o sistema em qualquer lugar e a qualquer momento recorrendo-se a interfaces ubíquas fornecidas através de dispositivos móveis ou Internet. Em segundo lugar, os dados recolhidos devem ser armazenados numa plataforma que garanta a segurança, integridade, e acesso aos dados a pacientes e a profissionais de saúde. Em terceiro lugar, o sistema deve apoiar a tomada de decisão clínica dos profissionais de saúde, através da apresentação de informação baseada nos dados obtidos ou em previsões que podem originar ajustes na terapêutica de cada paciente. Além disso, o sistema deve gerar alertas em tempo real e mensagens para pacientes e profissionais de saúde.

A sustentabilidade deste argumento, foi realizada de acordo com a seguinte abordagem.

O problema e a área de investigação foram estudadas tendo em conta dois temas distintos: sistemas de monitorização ubíquos (por exemplo, sistemas móveis e baseados na Internet) e tecnologias de computação envolvidas em sistemas de apoio à decisão clínica para a gestão da dor (por exemplo, técnicas de aprendizagem automática). Para ambos os temas a literatura foi revista de forma sistemática com o objetivo de se apresentar informação detalhada, bem como as principais vantagens e limitações de cada tecnologia e sistema.

A eficácia e a exequibilidade do sistema de monitorização proposto foi comprovada com a realização de um ensaio clínico envolvendo dois grupos de participantes divididos em grupo de tratamento em que foi usado o sistema proposto e o grupo de controlo. Os participantes foram recrutados ao longo de seis semanas no serviço ambulatório de pós-operatório do Hospital Sousa Martins. Durante o período de monitorização, cinco dias, os participantes do grupo de tratamento foram solicitados a introduzir o valor da intensidade da dor várias vezes por dia, em conformidade com o protocolo de tratamento definido pelo médico. Além disso, os participantes de ambos os grupos do estudo foram contactados pelos profissionais de saúde ao fim de 24 horas e no último dia de monitorização de forma a indicarem a dor média verificada. Todos os participantes preencheram questionários de pré e pós-estudo relacionados com o uso de telemóveis, acesso a registos eletrónicos de saúde, experiência decorrente do uso do software de monitorização proposto e ainda a opinião relativa à participação no estudo.

Finalmente, o modelo de apoio à decisão clínica, baseado nas condições dos pacientes e no seu autodiagnóstico combinados com regras e protocolos de tratamento definidos pelos profissionais de saúde, foi testado recorrendo-se aos dados obtidos quando da realização do ensaio clínico. O modelo proposto engloba a imputação de dados para os registos não preenchidos pelo paciente combinado com análise da variância e análise de discrepância de modo produzir alertas personalizados, relatórios e orientação à prática médica.

Principais Contribuições

A primeira contribuição desta tese é uma descrição detalhada das abordagens existentes de metodologias de aprendizagem automática e de técnicas de gestão de conteúdos através de uma revisão sistemática da literatura sobre tecnologias de computação envolvidas em sistemas de apoio à decisão clínica aplicados à gestão da dor. Este estudo está descrito em

detalhe no capítulo 2, que consiste num artigo aceite para publicação no Journal of Intelligent & Fuzzy Systems.

A segunda contribuição desta tese é a descrição detalhada das abordagens existentes relacionadas com os sistemas móveis e baseados na Internet através de uma revisão sistemática e uma meta-análise da literatura sobre sistemas computorizados de monitorização da dor crónica. Este estudo está descrito em detalhe no capítulo 3, que consiste num artigo submetido para publicação numa revista internacional com indexação ISI.

A terceira contribuição desta tese é a proposta de um modelo matemático para determinar o efeito decorrente da utilização de sistemas computorizados. Este modelo foi inspirado na capacidade dos sistemas aeroespaciais para lidar com múltiplas fontes de dados que por sua vez podem apresentar diferentes complexidades e precisões. Assim, é proposto um modelo de análise qualitativa decorrente da fusão de dados, combinado com um modelo quantitativo com base na comparação do desvio padrão com os valores das expectativas matemáticas. Este modelo foi brevemente introduzido no estudo apresentado no capítulo 3 e está descrito de forma exaustiva no capítulo 4, que consiste num artigo submetido para publicação numa revista internacional com indexação ISI.

A quarta contribuição desta tese é a proposta de um sistema computorizado para a monitorização da dor que compreende um PHR disponível online, um diário eletrónico de dor instalado no *smartphone* do paciente, e um sistema de apoio à decisão clínica, com capacidade para produzir relatórios em tempo real, alertas e *feedback* orientado a pacientes e a profissionais de saúde. O acesso à Internet permite a comunicação entre o paciente e o profissional de saúde em qualquer lugar e a qualquer momento, através da utilização de *web services*, garantindo-se assim um modo interoperável de acesso à informação. Este estudo está descrito em detalhe no capítulo 5, que consiste num capítulo de livro publicado em [59] como sendo uma versão alargada do artigo publicado em [60].

A quinta contribuição desta tese é o ensaio clínico realizado no Hospital Sousa Martins, que envolveu pacientes submetidos a intervenções cirúrgicas com probabilidade de ocorrência de dor durante o período pós-operativo. Diversas hipóteses foram analisadas no ensaio clínico, nomeadamente: a aceitação, satisfação e conformidade do sistema proposto e a sua contribuição na melhoria da qualidade dos tratamentos prestados. Este estudo está descrito em detalhe no capítulo 6, que consiste num artigo submetido para publicação numa revista internacional com indexação ISI.

A sexta contribuição desta tese é a proposta de um sistema de apoio à decisão clínica com base na imputação de dados combinada com modelos estatísticos, nomeadamente com a análise de variância (*one-way ANOVA* e *Kruskal-Wallis*) e análise de discrepância (*Tukey-Kramer*). Foi analisada a adequação e precisão deste modelo quando aplicado a tomadas de

decisão relacionadas com sintomas de dor. Este estudo está descrito em detalhe no capítulo 7, que consiste num artigo submetido para publicação numa revista internacional com indexação ISI.

Principais Conclusões

Esta tese é focada nas tecnologias de informação aplicadas à gestão da dor e descreve o trabalho de investigação desenvolvido com o objetivo de propor uma nova abordagem que oferece capacidades de ubiquidade e interoperabilidade. Os trabalhos de investigação visaram a complementaridade e a abrangência de modo a promoverem um aumento do conhecimento nos mais diversificados tópicos: revisão sistemática, meta-analise, ensaio clínico, capítulo de livro, artigo em conferência e *working paper*. Para além disso, o trabalho de investigação foi realizado de acordo com diversas normas e orientações, nomeadamente: *PRISMA statement*, *Cochrane Collaboration's tools*, *CONSORT statement* e *IMMPACT recommendations*.

Todas as premissas resultantes do trabalho de investigação foram testadas em laboratório e/ou em ambiente clínico, de modo a produzirem evidências inequívocas dos conceitos e técnicas propostas. Estas premissas foram baseadas na análise crítica dos sistemas suportados por dispositivos móveis e Internet conjuntamente com a análise das tecnologias de computação utilizadas pelos sistemas de apoio à decisão clínica para a gestão da dor. Além disso, um ensaio clínico foi implementado com o objetivo de validar o sistema de monitorização proposto enquanto que o modelo de apoio à decisão que é usado nesse sistema foi validado em laboratório através da utilização do *Microsoft Excel* combinado com o *IBM SPSS Statistics*.

Este procedimento de investigação resultou em contribuições desta tese que conduziu à realização do principal objetivo proposto referente ao desenvolvimento de um sistema de monitorização composto por interfaces ubíquas fornecidas através de dispositivos móveis e Internet, utilizando um repositório seguro para armazenamento dos dados, assegurado pela utilização de um PHR e complementado por um sistema de apoio à decisão clínica que gera alertas em tempo real e mensagens para pacientes e profissionais de saúde.

A inclusão efetiva de profissionais de saúde e pacientes conjuntamente com a capacidade de interoperabilidade e ubiquidade levantam preocupações e desafios para a conceção, desenvolvimento e aplicação de sistemas de monitorização da dor. A interação com o sistema a qualquer momento e em qualquer lugar oferece oportunidades para a prestação de cuidados de saúde, contribuindo para potenciar melhores tratamentos e resultados, baseados em

sistemas de monitorização que visam não só produzir resultados precisos, mas também otimizar os recursos humanos e materiais. Assim, as várias abordagens que têm sido propostas na literatura apresentam as seguintes limitações. Primeiro, grande parte dos sistemas computorizados são projetados para interagir diretamente com os pacientes sem a presença ou supervisão de profissionais de saúde. Em segundo lugar, a partilha e acesso à informação, dos profissionais de saúde, dos pacientes, ou de ambos é muitas vezes inexistente ou impraticável. Em terceiro lugar, estes sistemas são geralmente limitados em termos de integração de dados com dispositivos e/ou sistemas externos. Em quarto lugar, a fiabilidade e a precisão desses sistemas são raramente demonstradas. Em quinto lugar, o estudo sobre os efeitos da utilização de sistemas computorizados nos profissionais de saúde e pacientes permanece escasso.

Assim, o objetivo principal desta tese foi propor uma abordagem alternativa que não sofra as limitações acima mencionadas. Os objetivos secundários foram definidos, de modo a dividir o trabalho de investigação em componente teórica e prática como forma de se alcançar o objetivo principal. A componente teórica foi baseada no estudo das soluções existentes relacionadas com as tecnologias de computação utilizadas por sistemas de apoio à decisão clínica aplicados na gestão da dor. Este estudo apresenta as vantagens e limitações de cada solução de modo a produzir o estado da arte, com especial destaque na agregação de métodos de acordo com as diferentes técnicas de aprendizagem automática e a sua descrição, em termos de precisão, sintomas, enquadramento médico, decisões tomadas, ubiquidade e acessibilidade. A revisão da literatura revelou as seguintes metodologias: algoritmos baseados em regras, redes neuronais, *rough sets*, conjuntos difusos, e algoritmos estatísticos de aprendizagem. Além disso, terminologias, questionários e *scores* foram técnicas de gestão de conteúdos encontradas na literatura. Devido ao facto destas técnicas envolverem muitas variáveis dificulta a construção de modelos válidos por parte dos médicos especialistas, o que pode originar sistemas de baixa precisão que resultem em diagnósticos inadequados ou incorretos. Além disso, observou-se a inexistência de avaliação dos efeitos económicos e sociais resultantes da utilização destes sistemas. Por fim, o excessivo tempo despendido no preenchimento de questionários e *scores*, a falta de integração com dispositivos móveis, o uso limitado de interfaces baseadas em Internet e a escassez de sistemas que permitam a inserção de dados pelos pacientes foram limitações detetadas.
A componente teórica foi complementada pelo estudo das soluções existentes relacionadas com os sistemas móveis e Internet aplicados na gestão da dor crónica. Neste estudo os sistemas foram caracterizados nos seguintes tópicos: principais resultados apresentados, objetivos, sintomas dos pacientes, participantes, localização (por exemplo, casa do paciente, hospital, ...), dados recolhidos no âmbito do sistema, dados complementares ao sistema, e ainda a metodologia utilizada para transmitir dados entre o paciente e o profissional de saúde. Além disso, uma lista de 10 critérios foi desenvolvida para avaliar a qualidade dos sistemas. A revisão da literatura revelou a predominância de sistemas baseados em

dispositivos móveis (81%) em relação aos sistemas baseados na Internet (19%). Foi observada a utilização prévia, posterior ou durante o tratamento de aproximadamente noventa escalas e questionários. Os dados obtidos compreenderam, entre outros: a localização, duração e intensidade da dor, as consequências como o impacto na qualidade de vida, aspetos emocionais e aversivos. Isto não só evidencia a condição multidimensional da dor, como representa desafios e preocupações relacionados com a conceção, desenvolvimento e implementação de sistemas computorizados para a sua gestão. Este estudo também revelou que 44% dos sistemas transmitem os dados imediatamente após a sua aquisição, através da Internet, computador pessoal ou SMS, ao passo que 49% transmitem os dados com desfasamento temporal relativamente à sua aquisição, por exemplo apenas durante a consulta presencial ou no final do período de monitorização, tendo os restantes 7% não indicado o método de transmissão. Este estudo também apresentou um modelo inovador para avaliar o efeito da utilização de tecnologia, ou seja de sistemas computorizados, nas diferentes dimensões da dor. Este modelo baseia-se numa análise quantitativa resultante do método de fusão de dados em combinação com um modelo qualitativo com base na comparação do desvio padrão conjuntamente com os valores das expectativas matemáticas. Esta metodologia determina o efeito resultante da utilização da tecnologia em comparação com a abordagem tradicional em papel e foi aplicada a várias dimensões da dor. Observou-se que as duas abordagens produzem efeitos equivalentes nas dimensões: ansiedade, depressão, interferência e intensidade da dor. Pelo contrário, a tecnologia evidencia efeitos favoráveis em termos de catastrofização e incapacidade originada pela ocorrência de dor.

A componente prática foi baseada na avaliação do sistema proposto, que consistiu na realização de um ensaio clínico que envolveu pacientes em regime ambulatório de pós-operatório, complementado por investigação em laboratório com o intuito de se determinarem novos modelos de suporte à decisão clínica. O ensaio clínico foi realizado no Hospital Sousa Martins, tendo incluído a participação de 32 pacientes, com idades compreendidas entre 18 e 75 anos, com dor aguda resultante da intervenção cirúrgica. Os participantes foram recrutados durante um período de seis semanas e foram divididos em grupo de tratamento, que utilizou o sistema proposto e grupo de controlo. O estudo evidenciou não apenas que a maioria dos participantes recomendam o sistema, mas igualmente que eles reconhecem a sua adequação para a gestão da dor sem a necessidade de conhecimentos avançados em novas tecnologias. Além disso, o sistema permitiu a definição e a gestão de tratamentos orientados aos pacientes com reduzido tempo de intervenção do profissional de saúde. Foi evidenciado que o acompanhamento dos pacientes por parte dos profissionais de saúde na fase inicial da monitorização é determinante para a satisfação dos pacientes, influenciado a sua opinião quanto à recomendação do sistema e à sua utilidade na melhoraria da gestão da dor. Não se verificaram diferenças significativas entre o grupo de intervenção e o grupo de controlo, respeitante à melhoria da qualidade dos tratamentos prestados.

Com base nos dados obtidos durante a realização do ensaio clínico, foi desenvolvido um sistema de apoio à decisão de forma a complementar o sistema de monitorização proposto, através da emissão de alarmes personalizados, relatórios automáticos e indicações necessárias à orientação clínica. O sistema, denominado *Patient Oriented Method of Pain Evaluation System* (POMPES) é composto pelos seguintes componentes: entrada de dados, imputação de dados sempre que existam dados não definidos pelo paciente, análise de variância, análise de discrepância e saída de dados.

A entrada de dados é ajustada de acordo com o protocolo de tratamento e a duração da monitorização, podendo assim expressar diferentes granularidades, desde um único dia até uma semana inteira de dados de autodiagnóstico. A imputação de dados visa a atribuição de valores aos dados não preenchidos pelos pacientes através da estimação decorrente de uma regressão linear. A análise de variância utiliza o modelo *one-way ANOVA* caso os dados assumam uma distribuição normal (Gaussiana) ou o teste *Kruskal-Wallis* caso contrário. A análise da discrepância é determinada com base nos princípios de *Tukey-Kramer*, permitindo calcular a variação entre os diversos períodos de tratamento. Finalmente, a saída de dados inclui o resultado da comparação das diversas entradas em termos de significância estatística, a análise quantitativa resultante das comparações entre os múltiplos períodos de tratamento e ainda diversas métricas relativas à intensidade da dor, tais como valor máximo, mínimo, média diária, o valor inserido e o tempo decorrido desde o último preenchimento de dados por parte do paciente.

A combinação da imputação de dados com métodos estatísticos tais como *one-way ANOVA*, *Kruskal-Wallis* e *Tukey-Kramer* resultou numa total precisão em temos das decisões sugeridas pelo sistema em comparação com os diagnósticos proferidos pelos médicos. Assim, o sistema POMPES revelou adequabilidade para a gestão da dor, evidenciando capacidade para detetar, quer a estabilidade (caso padrão) como a mudança (caso excecional) da intensidade da dor.

O objetivo principal desta tese foi cumprido mediante a apresentação do sistema de monitorização. Este sistema permite o acesso ubíquo a profissionais de saúde e pacientes, de modo a que eles possam interagir com o sistema em qualquer lugar e a qualquer momento, usando-se *web services* para o envio e receção de dados. Além disso, os dados obtidos são armazenados num PHR, o que permite integridade e segurança dos dados, bem como o permanente acesso à informação a pacientes e profissionais de saúde. Este sistema é complementado por um sistema de apoio à decisão clínica, baseado num modelo matemático que fornece alertas em tempo real e mensagens orientadas a profissionais de saúde e pacientes, que resultam da análise dos dados obtidos conjuntamente com as parametrizações, tratamentos e protocolos definidos para cada paciente, possibilitando ao profissional de saúde um melhor controlo sobre a monitorização.

Direções Para Trabalho Futuro

Uma das linhas de investigação que poderá ser desenvolvida no futuro, prende-se com a avaliação dos custos decorrentes da aplicação do sistema proposto. A contribuição na melhoria da adesão dos pacientes às terapêuticas ministradas e a eficácia dos tratamentos são aspetos que poderão ser aprofundados através da realização de ensaios clínicos adicionais.

Além disso, ainda há oportunidades para melhorias no sistema de apoio à decisão clínica, mais concretamente com a sua execução na app que é instalada no *smartphone* do paciente. Em consonância com isso, o *workflow* do processo de decisão deverá ser repartido entre a app e o sistema de apoio à decisão clínica conjuntamente com o PHR.

Por fim, está prevista a realização de um ensaio clínico complementar envolvendo pacientes com dor crónica, tendo como objetivo a validação do sistema de apoio à decisão clínica proposto quando aplicado à monitorização durante um período de tempo alargado, o que poderá originar novos desenvolvimentos.

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Abstract

Millions of people around the world suffer from pain, acute or chronic and this raises the importance of its screening, assessment and treatment. The importance of pain is attested by the fact that it is considered the fifth vital sign for indicating basic bodily functions, health and quality of life, together with the four other vital signs: blood pressure, body temperature, pulse rate and respiratory rate. However, while these four signals represent an objective physical parameter, the occurrence of pain expresses an emotional status that happens inside the mind of each individual and therefore, is highly subjective that makes difficult its management and evaluation. For this reason, the self-report of pain is considered the most accurate pain assessment method wherein patients should be asked to periodically rate their pain severity and related symptoms. Thus, in the last years computerised systems based on mobile and web technologies are becoming increasingly used to enable patients to report their pain which lead to the development of electronic pain diaries (ED). This approach may provide to health care professionals (HCP) and patients the ability to interact with the system anywhere and at anytime thoroughly changes the coordinates of time and place and offers invaluable opportunities to the healthcare delivery. However, most of these systems were designed to interact directly to patients without presence of a healthcare professional or without evidence of reliability and accuracy. In fact, the observation of the existing systems revealed lack of integration with mobile devices, limited use of web-based interfaces and reduced interaction with patients in terms of obtaining and viewing information. In addition, the reliability and accuracy of computerised systems for pain management are rarely proved or their effects on HCP and patients outcomes remain understudied.

This thesis is focused on technology for pain management and aims to propose a monitoring system which includes ubiquitous interfaces specifically oriented to either patients or HCP using mobile devices and Internet so as to allow decisions based on the knowledge obtained from the analysis of the collected data. With the interoperability and cloud computing technologies in mind this system uses web services (WS) to manage data which are stored in a Personal Health Record (PHR).

A Randomised Controlled Trial (RCT) was implemented so as to determine the effectiveness of the proposed computerised monitoring system. The six weeks RCT evidenced the advantages provided by the ubiquitous access to HCP and patients so as to they were able to interact with the system anywhere and at anytime using WS to send and receive data. In addition, the collected data were stored in a PHR which offers integrity and security as well as permanent on line accessibility to both patients and HCP. The study evidenced not only that the majority of participants recommend the system, but also that they recognize it suitability for pain management without the requirement of advanced skills or experienced

users. Furthermore, the system enabled the definition and management of patient-oriented treatments with reduced therapist time. The study also revealed that the guidance of HCP at the beginning of the monitoring is crucial to patients' satisfaction and experience stemming from the usage of the system as evidenced by the high correlation between the recommendation of the application, and it suitability to improve pain management and to provide medical information. There were no significant differences regarding to improvements in the quality of pain treatment between intervention group and control group. Based on the data collected during the RCT a clinical decision support system (CDSS) was developed so as to offer capabilities of tailored alarms, reports, and clinical guidance. This CDSS, called Patient Oriented Method of Pain Evaluation System (POMPES), is based on the combination of several statistical models (one-way ANOVA, Kruskal-Wallis and Tukey-Kramer) with an imputation model based on linear regression. This system resulted in fully accuracy related to decisions suggested by the system compared with the medical diagnosis, and therefore, revealed it suitability to manage the pain. At last, based on the aerospace systems capability to deal with different complex data sources with varied complexities and accuracies, an innovative model was proposed. This model is characterized by a qualitative analysis stemming from the data fusion method combined with a quantitative model based on the comparison of the standard deviation together with the values of mathematical expectations. This model aimed to compare the effects of technological and pen-and-paper systems when applied to different dimension of pain, such as: pain intensity, anxiety, catastrophizing, depression, disability and interference. It was observed that pen-and-paper and technology produced equivalent effects in anxiety, depression, interference and pain intensity. On the contrary, technology evidenced favourable effects in terms of catastrophizing and disability. The proposed method revealed to be suitable, intelligible, easy to implement and low time and resources consuming. Further work is needed to evaluate the proposed system to follow up participants for longer periods of time which includes a complementary RCT encompassing patients with chronic pain symptoms. Finally, additional studies should be addressed to determine the economic effects not only to patients but also to the healthcare system.

Keywords

Pain: management, assessment, monitoring. Clinical decision support systems. Computing: mHealth, ubiquity, cloud, data fusion, data imputation. Web services. Personal Health Record.

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Acronyms

BAN	Body Area Network
CDSS	Clinical Decision Support System
ED	Electronic Diary
ECG	Electrocardiography
EEG	Electroencephalography
EMA	Ecological Momentary Assessment
HCP	Health Care Professionals
IT	Information Technologies
PD	Pen-and-paper Diary
PHR	Personal Health Record
RCT	Randomised Controlled Trial
WS	Web Services

Chapter 1

Introduction

This thesis addresses the subject of Information Technologies (IT) for pain management. The focus and scope of the thesis are further described in this chapter, together with the problem definition and objectives, the thesis statement, main contributions, and thesis organization.

1. Thesis Focus and Scope

According to the International Association for the Study of Pain [1,2], pain is an unpleasant sensory and emotional experience related to past or potential tissue damage or it may be described in terms of such damage. It is the oldest medical problem and the largest physical affliction of mankind, yet it has been little understood in physiology until very recently [3]. Furthermore, pain is the fifth vital sign for indicating basic bodily functions, health and quality of life [4,5], together with the four other vital signs: blood pressure, body temperature, pulse rate and respiratory rate. However, unlike these vital signs, pain does not represents an objective measurement but an emotional status that happens inside the mind of each individual and we can say more appropriately that we "estimate" or "translate" pain rather than measuring it. In addition, different conditions were experienced by patients according the duration of pain. When occurs with a relatively short duration it is known as acute pain, whereas persists over a long period of time it is regarded as chronic pain [6]. In both situations, pain is a highly subjective experience for each individual, denoting an awareness of noxious sensation in the mind's representation of self [7], that relies of physiological, neurological and psychological aspects. Therefore, it is not a simple entity but a multidimensional experience [8-12], that comprises sensory (e.g. location, intensity), affective (e.g. depression, anxiety) and cognitive (e.g. quality of life) aspects.

The occurrence of pain account for billions in annual medical expenditures [13], loss of quality of life and decreased worker productivity contribute to indirect costs [14–16]. When it persists over a long period of time, pain management is widely expensive due to the need of long-term rehabilitation in multi-disciplinary treatments [17], some of them usually administered to patients in their own homes (a.k.a. outpatients). Thus, measurement of pain is becoming increasingly important because it is recognized that pain is underestimated by health care professionals (HCP) and widely under-treated

[18–20], as evidenced by the current standards of the Joint Commission on Accreditation of Healthcare Organizations [21], which requires assessing and documenting pain in each patient, and its management provided by HCP adequately educated on pain. As self-report is considered the most accurate pain assessment method [22,23], patients should be asked to periodically rate their pain severity and related symptoms by completing scales and questionnaires. These reports are obtained for many different purposes such as: screening (e.g. admit, refer or discharge), diagnosis (e.g. disease prediction), treatment (e.g. pain management) and short or long term monitoring.

Systems that process data relating to pain are called pain diaries. These systems are the cornerstone of the monitoring of patients that suffer acute or chronic pain and initially the data were collected based on pen-and-paper diaries (PDs). Desirably the data collected by these systems should be further intelligently used by clinical decision support systems (CDSSs) so as to support HCP in screening, diagnosis and treatment decisions. Unsurprisingly therefore, that in the last years computerised systems were largely adopted to monitor patients that suffered with pain. These systems, called electronic diaries (EDs) not only represent a computerised version of PDs but also might enhance the scope of PDs so as to provide many different purposes, namely education, reminders, feedback, and disease control [24]. EDs are mainly delivered via mobile devices and Internet, which ubiquity raised the paradigm of the new care model based more on contacts than on visits [25]. On the one hand, the ability to interact with the system anywhere and at anytime thoroughly changes the coordinates of time and place and offers invaluable opportunities to the healthcare delivery. On the other hand, mobile devices showed significantly advances in storage capacity, battery efficiency, portability [26] and ability to access internet-based resources [27], that increased its suitability to healthcare systems. The adoption of EDs enable patients either to report complaints close in time that pain occurs, called ecological momentary assessment (EMA), or to address retrospective pain, that consists in pain recall over some period of time.

However, the adoption of technology applied on the screening, diagnosis, treatment or monitoring of pain complaints raise several challenges. Firstly, how different users' profiles such as patients and HCP should interact with the system. Secondly, how the data are collected, stored, remain persistent and accessible. Thirdly, who parameterizes, monitors, analyses and produces decisions based on the collected data. Fourthly, how patients and HCP are informed about these decisions. Finally, how to determine the effect caused by the use of technology.

The scope of this thesis is limited to computerised systems that constitute CDSSs or EDs related to acute or chronic pain complaints, and include data about pain assessment or produce outcomes based

on pain occurrences on screening, diagnosis, treatment or monitoring. The research work presented in this thesis is focused on the study of challenges raised by the application of IT for pain management, more specifically with the proposal of a system that allows the integration of EDs with CDSSs. The methodology proposed herein is based on ubiquity, interoperability and knowledge based decision so as to compose the computerised monitoring system. First, the ubiquity is verified by the use of an application software designed for mobile devices (a.k.a. app) and Internet. Second, the use of a Personal Health Record (PHR) and web services (WS) enable the interoperability that is required. Finally, the knowledge based decision is supported on mathematical models and is divided into two proposals: a decision support model embedded into the monitoring system and a methodology to evaluate the effects of computerised systems on different dimensions of pain.

2. Problem Definition and Research Objectives

The problem addressed in this thesis is the self-reporting of patients with pain complaints using an information system so as to obtain an accurate assessment of pain, and consequently to contribute to the improvement of practices provided by the HCP. Motivated by the impact of IT for pain management, the first studies aimed to characterize either CDSSs or EDs related to pain. At the beginning of this doctoral programme, the feasibility and accuracy of EDs compared to PDs was already a reality addressed by several published studies [28–36]. However some limitations were detected, namely that EDs were commonly designed to interact directly to patients without presence of a healthcare professional [37,38] and/or without evidence of reliability and accuracy. As above-mentioned, pain is a multifaceted experience, so its therapeutic tends to involve many healthcare professionals and different expertises, therefore it is desirable that patient information may be obtained and delivered both easily and safely (e.g. avoidance of medical examination redundancy, faster patient profile acquisition, and permanent storage of clinical records).

A few studies presented integrated solutions basically combining ED with PHR or third-party information systems, nonetheless are limited to mere data repository [32] or to restricted use within hospital environment [39,40]. Moreover, most studies use Body Area Network (BAN) [41], medical devices and sensors such as wrist activigraphy [42], electrocardiography (ECG) [43,44] or electroencephalography (EEG) [45]. However, ECG and EEG required HCP' supervision and specific conditions to produce accurate outcomes such as the immobility of the patient which limits its use in remote pain monitoring. Furthermore, connectivity between hardware and software, complexity of the network topology, implementation, maintenance and expansion costs are constraints that may limit the use of BAN to monitor patients suffering with pain.

In addition, the CDSSs proposed in the literature are also limited in terms of ubiquity and accessibility as is evidenced by the data access restrictions. Many systems only permit remote access, via mobile or web-based interfaces, to HCP [46–54] or those that also allow access for patients are limited to the insertion of disease history forms and questionnaires prior to consultation [55,56]. Finally, the complexity of medicine raise several challenges to the design, development and application of CDSSs [57]. It appears to be hard for medical experts to build valid models when too many variables affect the process, leading to the design of low accuracy systems (e.g. due to overspecialisation or overfitting [58]), and therefore inadequate or incorrect diagnosis [54].

The main objective of this thesis is to present a new computerised system for pain monitoring that comprises patients and HCP, and provides data integration between ED and CDSS. The proposed system should be suitable for monitoring of either acute or chronic pain patients, being able to produce real-time reports, alerts and feedback to HCP and patients based on comprehensible and adjustable mathematical models. Additionally, the proposed system should provide ubiquitous and interoperability access to collected data either to HCP or patients.

The following secondary objectives were defined so as to divide and organize the research work required to accomplish the main objective of this thesis:

1. To understand the existing solutions related to computer technologies used by CDSSs for pain management, describing the different approaches, their advantages and limitations in order to produce the state of the art, with special focus in the clustering of methods according the different machine learning techniques, and its description in terms of accuracy, symptoms, medical setting, main decisions, ubiquity, and accessibility.

2. To understand the existing solutions related to mobile and web-based systems for pain management, describing the different approaches, their advantages, limitations in order to complement the state of the art, highlighting the methodologies applied to collect and transmit data between patients and HCP.

3. To prove the effectiveness and feasibility of the presented computerised monitoring system, one of the purposes of this thesis is to implement a randomised controlled trial (RCT) that comprises ambulatory post-operative patients divided into treatment group that use the system and control group.

4. To present a new method capable to produce clinical decisions based on the patients' conditions and self-report data combined with treatments rules and protocols defined by the HCP, one of the purposes of this thesis is to implement a CDSS based on mathematical and/or machine learning concepts which should be developed with several criteria in mind such as: accuracy, feasibility and simplicity.

3. Thesis Statement

This thesis proposes a new approach for the monitoring of patients with pain complaints based on ubiquitous and interoperability information system. Specifically, the thesis statement is:

The multidimensional aspect and subjectivity of pain requires a technological solution that encompasses modules specifically oriented to HCP and patients. Firstly, patients may be able to interact with the system anywhere and at anytime using ubiquitous interfaces provided via mobile devices or Internet. Secondly, the collected data may be stored in a platform that ensures safety and integrity of data, likewise grant access for patients and HCP. Thirdly, the system may provide to HCP decisions based on either collected data or predictions which may result in timely adjustments oriented to each patient. In addition the system may generate real-time alerts and messages to HCP and patients.

To support this thesis statement, the following research approach was adopted.

The problem and research field was studied and comprised two different topics: ubiquitous monitoring systems (e.g. mobile and web-based systems) and computer technologies (e.g. machine learning techniques) involved in CDSSs for pain management. For both, the literature was systematic reviewed so as to present detailed data, as well the main advantages and limitations of every approach.

The analysis of the computer techniques applied to pain management enabled the identification of two main clusters: machine learning and content processing. The explanation of these different approaches allowed the characterisation of CDSS in terms of knowledge base structure and inference engine. Moreover, the study included the analysis the ubiquity and human-interaction with the system as well as the reported accuracy.

In addition, the analysis of the mobile and web-based systems enabled the characterization of ubiquitous monitoring systems in terms of collected and processed information, namely in identifying

the questionnaires and scores used by HCP and patients. Furthermore, the study included a quality evaluation of the selected studies and presented a novel assessment methodology of monitoring systems which is based on data fusion combined with a qualitative assessment. This model was applied on the different dimensions of pain such as: anxiety, catastrophizing, depression, disability, interference and pain intensity.

To determine the effectiveness of the proposed computerised monitoring system, a RCT was implemented. The study comprised two groups of participants divided into treatment group that used the proposed system and control group. The participants were recruited over a six weeks period through specialty care physician referral from the ambulatory post-operative service. During the 5-days monitoring period, participants of treatment group were called to answer the pain intensity several times per day in accordance with the treatment protocol defined by the physician. In addition, participants in both arms of the study were called after 24 hours and at fifth day follow-up by the HCP and were asked to rate their recalled average pain. Both groups filled a pre and post-treatment questionnaires related to the use of mobile phones and computerised health services, experience on the usage of the proposed monitoring software and on study participation.

Finally, the proposed clinical decision model based on the patients' conditions and self-report data combined with treatments rules and protocols defined by the HCP was tested using the sample data resulted from the above mentioned RCT. The model encompasses data imputation, analysis of variance (parametric and non-parametric) and analysis of discrepancy so as to produce tailored alarms, reports, and clinical guidance. In addition, the mathematical foundations of these statistic models were presented.

4. Main Contributions

This section describes the main scientific contributions resulting from the research work presented in this thesis.

The first contribution of this thesis is a detailed description of the existing approaches consisting on machine learning and content management techniques based on a comprehensive analysis and systematic review of the literature on computer technologies involved in CDSSs applied to pain and its overall accuracy. The design of CDSS were detailed in the following topics: clinical conditions (e.g. acute or chronic pain symptoms), clinical settings (e.g, single or multi-centre, inpatients or outpatients, ...), tasks (screening, diagnosis, treatment or risk assessment), main decision and accuracy. Moreover, each system was described in terms of accessibility (e.g. to HCP, patients or

both), ubiquity and connectivity with other systems. This study is described in chapter 2, which consists of an article accepted for publication in Journal of Intelligent & Fuzzy Systems.

The second contribution of this thesis is a detailed description of the existing approaches related to mobile and web-based systems supported by a comprehensive analysis and systematic review of the literature on computerised systems for chronic pain monitoring. These systems were characterised in the following topics: reported key findings, objectives, patients conditions, participants, location (e.g. patient home, hospital, ...), data collected within the system, data complementary to the system, and the methodology used to transmit data between patients and HCP. The quality of systems was assessed using a defined list of 10 criteria. This study is described in chapter 3, which consists of an article submitted for publication in an ISI-indexed international journal.

The third contribution of this thesis is the proposal of a method to determine the effect of computerised systems. This model was inspired in the well-known capabilities of aerospace systems to deal with different complex data sources with varied complexities and accuracies. Thus, it results from a qualitative analysis model stemming from the fusion of data combined with a quantitative model based on comparison of the standard deviation together with the values of the mathematical expectations. This model was initially introduced in the study presented in chapter 3, and is described in chapter 4, which consists of an article accepted for publication in the journal Informatics for Health and Social Care.

The fourth contribution of this thesis is the proposal of a computerised system for pain monitoring that comprises a web-based PHR, an ED installed in the patients' smartphone, and a decision support model with capability to produce real-time reports, alerts and feedback to HCP and patients. Internet access is required to enable communications between patients and HCP anywhere and at anytime using WS and thus to ensure an interoperable mean to access information. This study is described in chapter 5, which consists of a book chapter published in [59] as an extended version of the paper published in [60].

The fifth contribution of this thesis is the RCT conducted at the Hospital Sousa Martins that comprised patients submitted to surgical procedures from which a certain degree of pain is expected or possible during the initial post-operative days. Several hypotheses were analysed such as: acceptability, satisfaction, and compliance of the proposed computerised system, and it contribution to increase the quality of pain treatment in ambulatory surgery. This study is described in chapter 6,

which consists of an article article accepted for publication in the journal Technology and Health Care.

The sixth contribution of this thesis is the proposal of a CDSS based on statistical models which combines data imputation, analysis of variance (one-way ANOVA or Kruskal-Wallis) and analysis of discrepancy (Tukey-Kramer). The suitability and accuracy of this model when applied to clinical decisions related to pain symptoms, were analysed. This study is described in chapter 7, which consists of an article submitted for publication in an ISI-indexed international journal.

5. Thesis Organization

This thesis is organized in eight main chapters. With the exception of the first, fifth and eighth chapters which presenting the introduction, an article published as a book chapter, and conclusions and future work, each of the main chapters is formed by an article published in or submitted to an international journal indexed in ISI.

To maintain the consistency with the remaining chapters, the Introduction chapter presents the reference list and the long form of an acronym is repeated in the first occurrence.
The subjects and organization of the main chapters of this thesis can be summarized as follows.

Chapter 1 describes the context of this thesis, explaining the scope and focus of the research work and presenting the problem addressed by the thesis and the objectives to be accomplished, as well as the thesis statement and the adopted approach for solving the problem. A summary of the main contributions of this thesis is also included, followed by the description of the organization and structure of the thesis.

Chapter 2 provides a systematic review of the published work on CDSSs for pain management, presenting the motivation and a brief background for pain assessment and monitoring, and focusing on the different approaches for machine learning and content management, highlighting their advantages and limitations. The detailed description of these systems and its accuracy are provided.

Chapter 3 provides a systematic review and meta-analysis of the published work on pain monitoring, presenting the motivation and a brief background for pain assessment and monitoring, and focusing on the different approaches for mobile devices and web-based systems. The detailed description of these systems, a quality assessment, and their potentialities and risks are provided. In addition,

meta-analysis is oriented to different dimensions of pain and is supported using a proposed mathematical model that combines data fusion and statistics.

Chapter 4 follows the work described in the previous chapter, focusing on the definition of a new model to determine the effect of computerised systems based on the comparisons of the outcomes obtained from the use of ED and PD. The topic of data fusion is introduced together with the mathematical definitions that support the proposed model. Moreover, a case study is presented and the results obtained are presented along with the discussion of the main observations.

Chapter 5 introduces the topic of WS, presenting its basis concepts, request-response message example, advantages, and promising improvements when applied to monitor of patients suffering with pain. Moreover, the workflow of the proposed computerised system is explained in detail.

Chapter 6 provides a RCT conducted at the Hospital Sousa Martins which main purpose is to evaluate the feasibility of a remote monitoring system in ambulatory post-operative pain. The proposed system is detailed and further explanations are provided. In addition, observed advantages and limitations are presented.

Chapter 7 follows the work described in the previous chapter, focusing on mathematical concepts that enable to extend the CDSS of the proposed computerised system. The description and comparison of mathematical models used by CDSSs are provided. In addition, the validation of the proposed model based on data imputation and statistical methods is presented as well as its advantages and limitations.

Chapter 8 presents the most important conclusions and contributions of this thesis and discusses directions for future research work.

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Chapter 2

Applied Computer Technologies in Clinical Decision Support Systems for Pain Management: A Systematic Review

This chapter consists of the following article:

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Applied Computer Technologies in Clinical Decision Support Systems for Pain Management: A Systematic Review

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Abstract. Millions of people around the world suffer from pain, acute or chronic and this raises the importance of its screening, assessment and treatment. Pain, is highly subjective and the use of clinical decision support systems (CDSSs) can play an important part in improving the accuracy of pain assessment, and lead to better clinical practices. This review examines CDSSs, in relation to computer technologies and was conducted with the following electronic databases: CiteSeer[x], IEEE Xplore, ISI Web of Knowledge, Mendeley, Microsoft Academic Search, PubMed, Science Accelerator, Science.gov, ScienceDirect, SpringerLink, and The Cochrane Library. The studies referenced were compiled with several criteria in mind. Firstly, that they constituted a decision support system. Secondly, that study data included pain values or results based on the detection of pain. Thirdly, that they were published in English, between 1992 and 2011, and finally that they focused on patients with acute or chronic pain. In total, thirty-nine studies highlighted the following topics: rule based algorithms, artificial neural networks, rough and fuzzy sets, statistical learning algorithms, terminologies, questionnaires and scores. The median accuracy ranged from 53% to 87.5%. The lack of integration with mobile devices, the limited use of web-based interfaces and the scarcity of systems that allow for data to be inserted by patients were all limitations that were detected.

Keywords: Clinical decision support system, pain measurement, medical informatics, machine learning

1.Introduction

Clinical decision support systems (CDSSs) are designed to assist healthcare professionals in decision-making tasks. These systems are widely used in countless healthcare processes such as triage, early detection of diseases, identification of changes in health symptoms, extraction of patient data from medical records, in-patient support, evaluation of treatment and monitoring. A general model of CDSS encompasses the following components: input, output, knowledge base and inference engine. The input (user interface) ensures that the clinical information is entered into the CDSS, whereas the output presents the decisions and/or suggestions provided by the system. The knowledge base contains the medical information which comprises for example rules and probabilistic associations while the inference engine includes formulas for combining the rules and associations [1]. These two components are critical in the design of a CDSS and its combination is chiefly important to ensure the generation of medical advices based on patient data [2]. In addition, CDSSs face additional challenges when applied to patients with symptoms of pain.

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According to the International Association for the Study of Pain [3,4], pain is an unpleasant sensory and emotional experience related to past or potential tissue damage or it may be described in terms of such damage. Furthermore, pain is the fifth vital sign for indicating basic bodily functions, health and quality of life [5,6], together with the four other vital signs: blood pressure, body temperature, pulse rate and respiratory rate. The symptom of pain can be distinguished according to its duration. When occurring with a relatively short duration it is known as acute pain. However, when pain persists over a long period of time it is regarded as chronic pain [7]. In both situations, pain is a highly subjective experience for each individual, and this makes it harder to produce an assessment that leads to the right treatments [8]. We are not measuring an objective physical parameter but an emotional status that happens inside the mind of each individual and we can say more appropriately that we "estimate" or "translate" pain rather than measuring it.

Nevertheless, apart from the philosophical considerations, the occurrence of pain diminishes the quality of life and working abilities of people [9]. Moreover, in accordance with findings from the US Committee on Advancing Pain Research [10], chronic pain alone, affects at least 116 million American adults (circa 37% of the total population), exceeding the total affected by heart disease, cancer, and diabetes combined. This results in costs for the country of up to $635 billion dollars each year in medical treatment and lost productivity.
Therefore the CDSSs should be developed to ensure that, despite the subjectivity of pain, these clinical tools can be used to improve patients' health and well-being through the intelligent application of resources. This study aims to describe CDSSs applied to pain management focusing firstly on computer technologies, and secondly on medical conditions, clinical settings, main decisions, and system accessibility. In addition, this study presents the sample size and the percentage of decisions produced by each system that are in line with medical decisions also known as accuracy.

2.Methods

2.1.Research Questions

The primary questions of this review were (RQ1) which computer technologies have been used in CDSSs applied to pain? (RQ2) What is the overall accuracy of these technologies?

2.2.Inclusion Criteria

Studies measuring and assessing pain using CDSSs were included in this review if they met the following criteria. (1) Constituted a decision support system, (2) related to acute or chronic pain complaints, (3) included data about pain values or (4) the system produced results based on the detection of pain occurrences, (5) used computerised systems, (6) were published between 1992 and 31st December 2011, and (7) were written in English. There were no age or disease restrictions: participants could be adults or children, chronic pain patients, healthy individuals with pain complaints, or individuals experiencing an episode of acute pain.

2.3.Search Strategy

The team searched for studies, meeting the inclusion criteria in the following electronic databases: CiteSeer[x], IEEE Xplore, ISI Web of Knowledge, Mendeley, Microsoft Academic Search, PubMed, Science Accelerator, Science.gov, ScienceDirect, SpringerLink, and The Cochrane Library. One study, [11] was published online (November 2011), while the team was researching the electronic databases and therefore qualified for this review. The study was subsequently published in February 2012.

Every study was independently evaluated by two reviewers (NP and PA) and its suitability determined with the agreement of both parties. A third reviewer was considered to adjudicate on differences of opinion but was not required because a consensus was reached. The studies were also examined to identify and isolate clusters reporting the same data, so as to avoid the risk of bias [12]. When different studies reported the same CDSS, they were considered independently since they comprised the different marked symptoms and approaches (e.g. the studies [13] and [14], relative to the CDSS of [15–20]).

Also, the references of the studies were analysed for any additional CDSSs studies applied to pain. The abstracts and/or full text papers of these studies were subsequently evaluated by both reviewers, following the same criteria they applied to the database searches.

2.4.Extraction of Study Characteristics

The data extracted from the studies, were tabulated (see Table 1) and comprised the following characteristics: year of publication, clinical information (i.e. condition, setting, task, decision, and improvement in practitioner diagnosis) and system information (users and ubiquity). The studies were separated into machine learning (ML) and content processing (CP). The ML (see Table 2) comprised rule based algorithms (RBA), artificial neural networks (ANN), rough and fuzzy sets (RFS), and statistical learning algorithms (SLA). The ML characteristics included study identification, year of publication (the earliest year, where studies reported from the same dataset), healthcare condition, number of learning/training/testing records, and accuracy (percentage of system decisions that are in line with medical decisions). The CP encompassed terminologies, questionnaires, and scores (see Table 3). The CP characteristics included study identification, year of publication, healthcare condition, number of records and type of content used. Each study and its content can be referenced across a wide and diverse range of ML and CP topics.

3.Results

As illustrated in Figure 1, our review identified 1,245 citations, of which 75 were duplicates. The remaining 1,170 citations were evaluated, in terms of title, abstract, and keywords, resulting in the exclusion of 1,081 citations because they clearly did not meet the inclusion criteria. Full text evaluation of the remaining 89 papers resulted in the exclusion of 57 papers that did not match the defined criteria. In addition, the reference tracking allowed for the

inclusion of seven additional papers. In summary then, our review examined 39 papers, representing 31 unique studies, because where studies reported the same data, they were clustered to avoid risk of bias.

As shown in Table 1, the most representative symptoms were abdominal pain, reported in ten studies (32%), chest pain, included in eight studies (26%), followed by low back pain and palliative care with three studies each (10%). These symptoms represented 78% overall. Meanwhile, the remaining symptoms comprised knee pain, with two studies, cancer pain, myofascial pain, post-operative pain, rheumatoid arthritis pain, and scrotal pain, all contained in one single study. Moreover, nine of the thirty-one studies (29%) included in this review were published before or during 2000, and of the remaining 22 studies, only seven were published by the end of 2005 (23%). Finally, 15 studies (48%) were published between the beginning of 2006 and the end of 2011.

Sixteen studies (52%) related to emergency care (EC), and six studies (19%) highlighted primary care (PC). Secondary/tertiary care which includes in-patient care and out-patient care were both reported in three studies (19%). The subject of in-patient and out-patient care was proposed by two studies whereas PC and out-patient care was suggested by just one study. The clinical tasks were divided among diagnosis (17 studies, 55%), treatment (six studies, 19%), screening (five studies, 16%) and risk assessment (three studies, 10%).
In addition, 25 studies presented results in terms of practitioner performance, of which 84% reported improvements in this area. Only four studies (13%) presented systems with patient interaction capabilities. The development of web-based CDSSs was reported in six studies (19%), and the usage of mobile devices was proposed in two studies (6%). SLA was the most commonly used technology with 13 of 31 studies (42%), followed by RBA with seven studies (23%) and ANN with six studies (19%).

Finally, RFS and terminologies were both applied in five studies (16%), and questionnaires and scores in two (6 %). The period from the beginning of 2006 until the end of 2011 showed an absence of studies using ANN. In this period, RBA and terminologies, with three studies each, appeared immediately behind SLA, which remained the most used technology with seven studies.

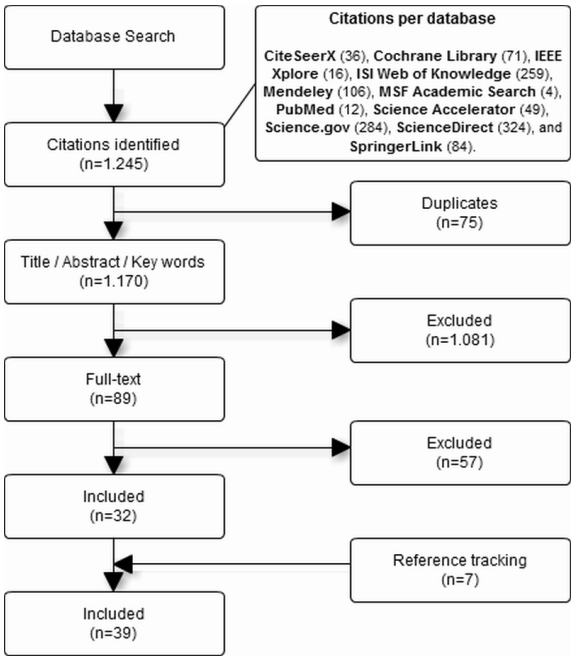

Figure 1: Flow diagram of identification and inclusion of papers

Table 1 - Selected Studies

Study	Year	Clinical							System	
		Condition	Setting			Task	Decision	IPP	Users	Ubiquity
Fathi-Torbaghan [21]	1994	Abdominal pain	A	PC	SC	Diagnosis	Prediction of the presence of abdominal pain	Yes	Physicians	
Blazadonakis [22]	1996	Abdominal pain	A	EC	SC	Diagnosis	Triage of patients in emergency: discharge, follow-up or operate	No	Physicians	
Ohmann [23]	1996	Abdominal pain	A	EC	MC	Diagnosis	Prediction of the presence of abdominal pain	No	Physicians	
Eich [24]	1997	Abdominal pain	A	EC	MC	Diagnosis	Prediction of the presence of abdominal pain	-	Physicians	
Ellenius [25,26]	1997	Chest pain	A	EC	MC	Diagnosis	Myocardial infartion prediction	Yes	Physicians	
Kennedy [27]	1997	Chest pain	A	EC	MC	Diagnosis	Myocardial infartion prediction	Yes	Physicians	
Pesonen [28]	1998	Abdominal pain	A	EC	MC	Diagnosis	Acute appendicitis prediction	No	Physicians	
Vaughn [29]	1998	Low back pain	C	PC	SC	Diagnosis	Classify into classes: Simple Low Back Pain, Root Pain or Abnormal Illness Behaviour	Yes	Physicians	
Aase [30]	1999	Chest pain	A	EC	SC	Diagnosis	Acute ischemic heart disease prediction	Yes	Physicians	
Wang [31]	2001	Chest pain	A	EC	MC	Diagnosis	Myocardial infartion prediction	Yes	Physicians	
Baxt [32]	2002	Chest pain	A	EC	SC	Diagnosis	Myocardial infartion prediction	Yes	Physicians	
Kuziemsky [33]	2003	Palliative care	C	SI	MC	Treatment	Pain management	-	Physicians, Nurses	
Wilkie [34,35]	2003	Cancer pain	C	SI/SO	MC	Treatment	Score and interpretation of McGill Questionnaire	Yes	Physicians, Patients	Mobile devices

Study	Year	Clinical							System	
		Condition		Setting		Task	Decision	IPP	Users	Ubiquity
Farion-Michalowski [15–20]	2004	Abdominal pain	A	EC	SC	Screening	Triage of patients in emergency: discharge, observation or consult	Yes	Physicians, Nurses	Web-based interface [20], and mobile devices [19]
Blaszczynski [14]	2005	Abdominal pain	A	EC	SC	Screening	Triage of patients in emergency: discharge, observation or consult	Yes	Physicians, Nurses	
Farion-Michalowski [13]	2005	Scrotal pain	A	EC	SC	Screening	Triage of patients in emergency: discharge, observation or consult	Yes	Physicians, Nurses	
Lin Lin [36]	2006	Low back pain	C	SO	MC	Diagnosis	Classify patients with low back pain	Yes	Physicians	Web-based interface
Sadeghi [37]	2006	Abdominal pain	A	EC	SC	Screening	Triage of patients in emergency : admit, refer or discharge	Yes	Nurses	
Westfall [38]	2006	Chest pain	A	EC	MC	Diagnosis	Acute ischemic heart disease prediction	No	Physicians, Nurses	
Chang [39]	2007	Palliative care	C	SI/ SO	SC	Treatment	Pain management	-	Physicians, Nurses, Patients	Integration with EMR/ PHR
Lai [40]	2007	Knee pain	C	PC	SC	Diagnosis	Patellofemoral pain syndrome prediction	Yes	Physicians	
van Gerven [41,42]	2007	Abdominal pain	A	PC	SC	Risk assessment	Carcinoid heart disease prediction	Yes	Physicians	
Binaghi [43]	2008	Myofascial pain	A	PC	MC	Diagnosis	Temporomandibular disorders prediction	Yes	Physicians, Patients	Web-based interface
Elvidge [44]	2008	Palliative care	C	SI	SC	Treatment	Pain management	-	Physicians	Web-based interface
Hsin-Min Lu [45]	2008	Abdominal pain	A	EC	SC	Screening	Classify patients into syndromic categories	Yes	Physicians, Nurses	
Watt [46]	2008	Knee pain	C	SO	MC	Diagnosis	Prediction of the presence of knee pain	Yes	Physicians	
Abas [47]	2011	Postoperative pain	A	SI	-	Treatment	Pain management	-	Physicians, Nurses	Integration with HIS
Farooq [48]	2011	Chest pain	A	PC / SO	SC	Risk assessment	Chest pain risk assessment	-	Physicians, Patients	Web-based interface
Jinglin [49]	2011	Low back pain	C	SO	SC	Diagnosis	Prediction of the presence of low back pain	Yes	Physicians	
Kong [11]	2011	Chest pain	A	EC	SC	Risk assessment	Chest pain risk assessment	Yes	Physicians	Web-based interface
Simonic [50]	2011	Rheumatoid arthritis pain	C	PC	SC	Treatment	Pain management	Yes	Physicians	

A: Acute pain; **C**: Chronic pain;
EC: Emergency Care; **PC**: Primary Care; **SI**: Secondary/Tertiary In-patient Care; **SO**: Secondary/Tertiary Out-patient Care;
SC: Single Center; **MC**: Multi-Center;
IPP: Improvement in Practitioner Performance
-: None Reported

As shown in Table 2, Bayesian network, logistic regression and fuzzy logic presented the higher accuracy of medical diagnoses (100%). The rough set presented the best performance in terms of screening process (77%), whereas classification and regression tree (CART) revealed the best accuracy of risk assessment algorithms (80%). However, these values should be interpreted with caution due to the fact that they did not result from the comparison among different techniques and algorithms.

3.1.Rule Based Algorithms

Several RBA were found, namely AQ15 [51], C4.5 [52], CART [53], CN2 [54], ID3 [55], NewId [56], ITRULE [57], PRISM [58], and Inductive Learning by Logic Minimization (ILLM) [59]. The ID3 requires the building of a decision-tree based on rules relating to the choice of attributes. In turn, the C4.5 is based on the ID3, but with extended capabilities, achieved by pruning irrelevant branches of the decision tree. The NewId, also based on ID3, supports structured attributes and ordering [23]. In addition, the PRISM, based on ID3, aims to find just the relevant values of attributes, unlike ID3, which finds one overall attribute, regardless of its relevance and values. The AQ15 aims to remove redundant conditions from the initial rules set [51], while the CN2, based in both ID3 and AQ15, is used to improve the quality of the rules by evaluating and selecting the best ones. The CART is an algorithm that seeks to identify the most significant variables and discards the non-significant ones. Furthermore, the ITRULE searches the space for possible rules and evaluates the information content to establish a ranking [23,60].

Finally, ILLM is designed to find the minimal logic expression that represents the largest cases of the initial rules set. The clarity and understanding that the classification system gives represents the main advantage of the decision trees [61,62]. However, some limitations arise such as the overspecialisation [63,64] or the inefficiency for learning rules from incomplete data [65]. Moreover, the complexity of the clinical problem presents a barrier to reliable estimates of probabilities and decision criteria [23,66].

3.2.Artificial Neural Networks

The ANN are composed of interconnected processing elements, called nodes that carry out the classification process. These systems generate an output set where each element represents a particular classification for the input set. This is achieved via the propagation of estimated weights through the nodes of the network. Accordingly, [25,26] reported a system based on the usage of Single-Layer Perceptrons (SLP) [67] in parallel, also known as multiple-SLP (MSLP). Alternatively, [27–29,31,32] described a Multi-Layer Perceptrons approach (MLP) [68]. The SLP is applied to learning from a batch of training, in a repeated way, to find the accurate vector for the entire training set, whereas MLPs aim at the separation of input instances into their appropriate categories. However, despite its robustness to noisy data and its ability to represent complex functions [61,69], its inability to explain decisions and the lack of transparency of data [27,61,64,70], presents an obstacle for its use in clinical settings. Also,

determining the adequate size of the hidden layer is vulnerable to poor approximations (caused by lack of neurons) or overfitting (from excessive nodes) [69,71,72].

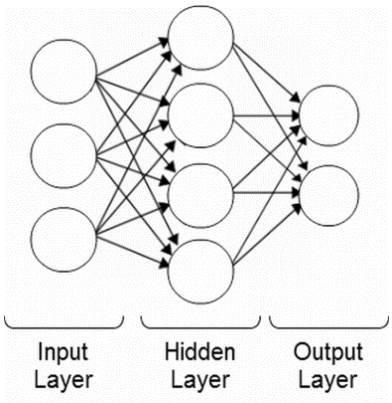

Figure 2: Illustration of an MLP

3.3.Rough and Fuzzy Sets

The rough set theory [73] proposed by [13–20] comprises a combination of two sets – namely lower and upper approximation. The lower approximation is made up of elements that do belong to the set, whereas the upper approximation is composed of elements that possibly belong to the set. The difference between them results in the boundary region of the rough set. This theory is limited when data tends to be noisy [74] and inefficient computation restricts its suitability for large data sets [74,75]. The main advantage is that it does not need any preliminary or additional information about data [76]. The fuzzy logic [77] represents a probabilistic logic model that uses reasoning to explain whether an event is about to happen. This model was introduced by [21,43] with the advantage that it allows for the use of vague linguistic terms in the rules [78,79]. However it is difficult to estimate the membership functions [80].

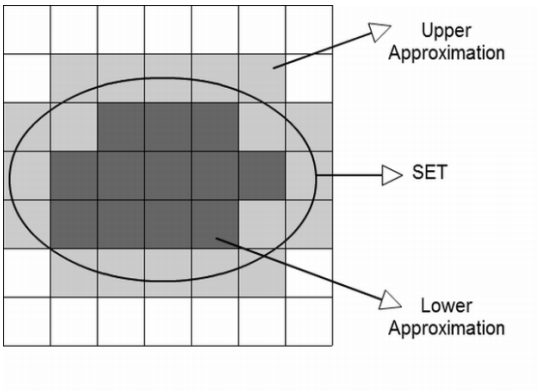

Figure 3: Illustration of a rough set

3.4.Statistical Learning Algorithms

The purpose of SLA is to learn structures of interest of a given data set [81]. The learning process occurs through prediction or description of input variable associations. The prediction, pre-supposes the completion of classification and regression tasks, whereas the description searches the data analysis to find some intrinsic structures. In line with this, [23,30,36] presented the Bayes' theorem (a.k.a. Bayes' rule) [82] which is a method of inference to precise the subjective degree of belief. This model is time-consuming and requires a thorough knowledge of its parameters [11].

In turn, the naive Bayes [83], applied by [14,22,41,42], is based on Bayes' theorem and assumes that the effect of a predictor in a class is independent relative to the values of other predictors. This model aims at reducing the computational time required by removing irrelevant or correlated parameters [64].
Bayesian network [84], comprises a directed acyclic graph, that includes arrow points (only one direction), no circular paths and nodes that represent a conditional probability value. This model was applied by [37,46] and is in many ways superior to RBA [37], because it defines probabilistic representations of uncertain knowledge [37,64]. By contrast, [41,42] suggested the use of Noisy-OR [85,86] and a simplification of this model, called Noisy-Threshold [87] that delivers a probabilistic approximation, to minimise the number of required parameters.

Other techniques were described, including k-Nearest Neighbour (kNN) [88], proposed by [44], IB1 [89], presented by [14], and Logistic Regression (LR) [90], used by [31,32,41,42,46]. The kNN consists of a multi-dimensional space, in which each element is plotted according to its own attribute values. Also, kNN requires large storage, is time-consuming, and is very sensitive to irrelevant parameters [91]. The IB1 is identical to the kNN, with a function that normalises its attributes' ranges, processes instances incrementally and can tolerate missing values [89]. In turn, LR is applied to model data where the target variable is binary and is designed to produce a model that allows for the prediction of assigned values to variables. This model is less susceptible to overfitting [92]. The weaknesses are its unsuitability to deal with non-linear problems and the interactive effects of variables [93].

Finally, as proposed by [40,49], the Support Vector Machine (SVM) [94] aims to map the training data to a higher dimensional space and separate the different classes of data, by constructing the optimal separating hyper-plane. This model has good generalisation ability and a robustness for high dimensional data [61,64]. The SVM is more suited to training and performs better compared to ANN [69]. However it is very sensitive to uncertainties [49,61], and a too high dimensional space can lead to overfitting of the data [69,95] and so slow the speed of the training [64,96].
The study reported in [49], uses an extended modelling method from SVM, called Probabilistic Support Vector Machine (PSVM), to handle uncertainties in data samples.

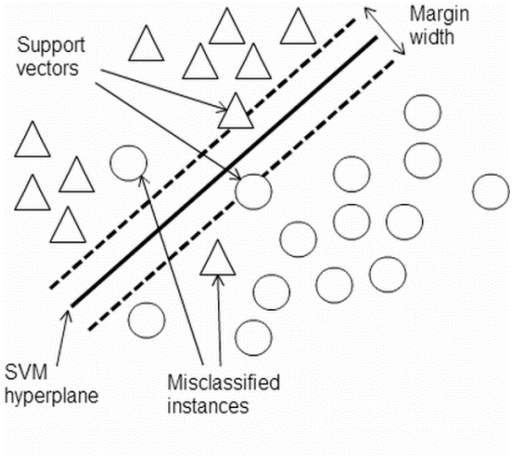

Figure 4: Illustration of a linear SVM decision function separating class+1 (*circles*) from the class-1 (*triangles*)

3.5.Questionnaires

As shown in Table 3, a computerised version of McGill Pain Questionnaire (MPQ) [97] was presented by [34,35] while [39] suggested a CDSSs based on patient-tailored questionnaires, that combined the Computerised Adaptive Testing (CAT) [98] with Item Response Theory (ITR) [99], to obtain the ideal arrangement of questions. The limitations were the time required to complete the questionnaire [24,34,35,50], and the time that elapsed between the editing and the occurrence of pain. This limitation also occurs in scores.

3.6.Terminologies

The Unified Medical Language System (UMLS) [100], reported by [33,47] (see Table 3), includes large health and biomedical vocabularies and also concepts extracted from several sources. These include; IDC9-CM [101], Logical Observation Identifiers Names and Codes (LOINC) [102], Medical Subject Headings (MeSH) [103], and Systematized Nomenclature of Medicine - Clinical Terms (SNOMED-CT) [104]. The UMLS was also proposed by [45] because it uses the Weighted Semantic Similarity Score (WSSS) [105] to exploit the semantic relationship between the reported symptoms and the UMLS terms. Also, [24,48] presented a system with a data dictionary based on SNOMED-CT terminology. However, several limitations were found. Firstly its complexity due to the high number of terms and relationships [106,107] and secondly the difficulty in integrating a new terminology [108].

3.7.Scores

The authors [38,50] (see Table 3) proposed CDSSs based on scores, resulting from the combination of several analysed characteristics. The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) [109], had no relevant impact on diagnostic screening nor did it contribute to improving the accuracy of chest pain patients as explained by [38]. The

Disease Activity Score (DAS) [110] together with Health Assessment Questionnaire (HAQ) [111] was proposed by [50] to optimise the patient treatments. The disadvantage of these systems is the time that is needed to obtain the required information [50].

Table 2 - Machine Learning: Rule Based Algorithms, Artificial Neural Networks, Rough and Fuzzy Sets, Statistical Learning Algorithms

Rule Based Algorithms

Study	Year	Condition	Number of Records		Algorithm	Accuracy
			Learn	Test		
Blazadonakis [22]	1996	Abdominal pain	268	67	AQ15	79%
					C4.5	84%
					CN2	86%
					NewId	73%
					ILLM	84%
Ohmann [23]	1996	Abdominal pain	839	415	C4.5	46%
					CN2	47%
					ID3	48%
					ITRULE	43%
					NewId	40%
					PRISM	45%
Eich [24]	1997	Abdominal pain	6815	3418	C4.5	57%
Blaszczynski [14]	2005	Abdominal pain	606	100	C4.5	57%
van Gerven [41,42]	2007	Abdominal pain	-	-	C4.5	44%
Elvidge [44]	2008	Palliative care	276	-	ID3 (with kNN)	-
Kong [11]	2011	Chest pain	1000	1000	CART	80%
Median			**722.5**	**415**		**57 %**

Artificial Neural Networks

Study	Year	Condition	Number of Records		Structure	Accuracy
			Learn	Test		
Ellenius [25,26]	1997	Chest pain	50	38	MSLP (3 SLPs)	90%
Kennedy [27]	1997	Chest pain	90	200	I/H/O: 53/18/1	92%
Pesonen [28]	1998	Abdominal pain	717	347	I/H/O: 16/6/3	78%
Vaughn [29]	1998	Low back pain	99	99	I/H/O: 92/10/3	67%
Wang [31]	2001	Chest pain	1253	500	I/H/O: 30/15/1	85%
Baxt [32]	2002	Chest pain	1050	926	I/H/O: 40/10/1	93%
Median			**408**	**273.5**		**87.5%**

Rough and Fuzzy Sets

Study	Year	Condition	Number of Records	Algorithm	Accuracy
Fathi-Torbaghan [21]	1994	Abdominal pain	100	Fuzzy logic	80%
Farion-Michalowski [15–20]	2004	Abdominal pain	328	Rough Set	66%
Blaszczynski [14]	2005	Abdominal pain	100	Rough Set	59%
Farion-Michalowski [13]	2005	Scrotal pain	30	Rough Set	77%
Binaghi [43]	2008	Myofascial pain	50	Fuzzy logic	100%
Median			**100**		**77%**

Statistical Learning Algorithms

Study	Year	Condition	Number of Records		Structure	Accuracy
			Learn	Test		
Blazadonakis [22]	1996	Abdominal pain	268	67	Naive Bayes	89%
Ohmann [23]	1996	Abdominal pain	839	415	Bayes' theorem	45%
Aase [30]	1999	Chest pain	493	290	Bayes' theorem	89%

Wang [31]	2001	Chest pain	1253	500	LR	84%
Baxt [32]	2002	Chest pain	2024	2024	LR	75%
Blaszczynski [14]	2005	Abdominal pain	606	100	Naive Bayes	56%
					IB1	58%
Lin Lin [36]	2006	Low back pain	180	20	Bayes' theorem	73%
Sadeghi [37]	2006	Abdominal pain	90	-	Bayesian network	56%
Lai [40]	2007	Knee pain	27	27	SVM	89%
van Gerven [41,42]	2007	Abdominal pain	-	-	Naive Bayes	63%
					LR	67%
					Noisy-OR	54%
					Noisy-Threshold	72%
Elvidge [44]	2008	Palliative care	276	-	kNN	-
Watt [46]	2008	Knee pain	4796	200	Bayesian network	100%
					LR	100%
Jinglin [49]	2011	Low back pain	21	21	PSVM	95%
					SVM	90%
Median			**384.5**	**150**		**74%**

-: None Reported; **I**: Nodes of input layer; **H**: Nodes of hiden layer; **O**: Nodes of output layer

Table 3 - Content Processing: Terminologies, Questionnaires, Scores

Terminologies				
Study	Year	Condition	Number of Records	Terminology
Eich [24]	1997	Abdominal pain	10233	SNOMED-CT
Kuziemsky [33]	2003	Palliative care	-	UMLS
Hsin-Min Lu [45]	2008	Abdominal pain	2256	UMLS
Abas [47]	2011	Post-operative pain	-	UMLS
Farooq [48]	2011	Chest pain	-	SNOMED-CT
Questionnaires				
Study	Year	Condition	Number of Records	Questionnaire
Wilkie [34,35]	2003	Cancer pain	213	MPQ
Chang [39]	2007	Palliative care	-	Patient-tailored
Scores				
Study	Year	Condition	Number of Records	Score
Westfall [38]	2006	Chest pain	1861	ACI-TIPI
Simonic [50]	2011	Rheumatoid arthritis pain	175	DAS, and HAQ

-: None Reported

4.Discussion

This review confirms the findings of previous studies across a range of topics. (1) Difficulty arising from the complexity of the systems**,** as reported by [112]. It appears to be hard for medical experts to build valid models when too many variables affect the process, leading to the design of low accuracy systems (e.g. due to overspecialisation or overfitting [23]), which may result in inadequate or incorrect diagnosis [36]. So the development and implementation of CDSSs may become more difficult due to their complexity [11]. (2) Opportunity to address therapy changes in a timely manner**,** as suggested by [113], derived from CDSSs implementation; and (3) difficulty in assessing the economic effects of CDSSs as described by

[114]. In fact, the absence of this assessment is confirmed in all studies. (4) In accordance with [115], only two studies provide integration with other systems such as HIS [116], EHR [117] or PHR [118].

New topics are also addressed by this review, namely: (5) content processing is primarily applied to the treatment of patients (5 of 9 studies). The patients can input data in two of these models whereas three allow for use by nurses. The main limitation of these models is (6) the excessive time required to complete the questionnaires and scores**.** (7) The diagnosis is mostly performed in EC (10 of 16 studies). Four studies note no improvement in practitioner performance, primarily due to the low accuracy rate [23] and poor clinical assessment procedures [22,28,38]. (8) All the screening systems are applied in EC (5 studies) and allow for use by nurses. Also, (9) lack of integration of the CDSSs with mobile devices (2 studies, 6%), and (10) reduced web-based interaction with the CDSS (6 studies, 19%). In addition, (11) the involvement of patients with the CDSSs is only verified in four studies (13%). Finally, (12) only ten studies are related to chronic pain (32%).

These topics suggest that the widespread availability and ubiquity of mobile devices and the Internet is not properly exploited by CDSSs. The ability to interact with the system anywhere and at anytime offers invaluable opportunities to physicians, health professionals and patients, which could lead to better and more efficient therapies. For example, these technologies could ensure the monitoring of patients in hospital or in ambulatory care with that data being included in the CDSS and being used to support the long term healthcare of chronic pain patients. Also, the inclusion of patients' data could take advantage of service oriented architecture (SOA) [119] and cloud computing [120] as proposed by [121], to obtain scalable and interoperable systems. The patients themselves could provide reports of their complaints and note the actual moment when pain occurs, also known as ecological momentary assessment (EMA) [122].

The inclusion of these data in the CDSSs could help address the use of unregulated electronic pain diaries, many of which are developed without medical supervision, or integration capabilities, or even evidence of their effectiveness [123]. Moreover, the regularly collected data could result in a more realistic assessment of the patient's health and consequently an accurate diagnosis. Thus, the weaknesses of CDSSs, mentioned by [124,125], regarding errors in diagnoses and decisions due to the difficulty of tracking patients' symptoms are likely to be minimised.

5.Conclusions

The purpose of this review was to distinguish CDSSs applied to patients suffering from pain, in relation to their computer technologies. Thirty-nine studies were examined and the main findings are summarised as follows:

(RQ1) the computer technologies that have been applied in CDSSs include machine learning and content processing. Machine learning encompasses rule based algorithms (RBA), artificial neural networks (ANN), rough and fuzzy sets (RFS), and statistical learning algorithms (SLA). Content processing comprises terminologies, questionnaires, and scores.

(RQ2) The ANN presented the higher median accuracy (87.5%), and thus outperformed RFS (77%), SLA (74%) and RBA (57%). Moreover, the Bayesian network, logistic regression and fuzzy logic presented the higher accuracy of medical diagnoses. The rough set presented the best performance in terms of screening process, whereas CART revealed the best accuracy of risk assessment.

In addition, the lack of integration with mobile devices, the limited use of web-based interfaces and the scarcity of systems that allow for data to be inserted by patients were all limitations that were detected.

5.1.Limitations

Some limitations of this review should be mentioned. First, the absence, by authors' choice, of studies focused on pain diaries. Second, some studies did not report clearly on data that are used for CDSSs (e.g. absence of number of records concerning learning and test sets, and/or accuracy value). Third, some studies presented skewed data, and this influenced their findings. Finally, only English-language publications were included.

5.2.Conflict of interest statement

No conflicts of interest.

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Chapter 3

Mobile and Web-based Systems for Chronic Pain Monitoring: A Systematic Review and Meta-analysis

This chapter consists of the following article:

Mobile and Web-based Systems for Chronic Pain Monitoring: A Systematic Review and Meta-analysis
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Mobile and Web-based Systems for Chronic Pain Monitoring: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Mobile and web technologies are becoming increasingly used in the treatment of chronic pain conditions. However, pain is highly subjective that makes difficult its management and evaluation. Its treatment requires a multi-dimensional approach (e.g. sensory, affective, cognitive) whence the evidence of technology effects across dimensions is lacking.

Purpose: To describe computerised monitoring systems and to suggest a methodology, based on statistical analysis, to evaluate their effects on different dimensions of pain.

Data Sources: BioMed Central, PubMed Central and ScienceDirect, from 2000 up until 30th June 2012

Study Selection: Investigators independently screened reports to identify studies published in English, of computerised systems related to chronic pain complaints that included data collected via mobile devices or Internet.

Data Extraction: Investigators extracted data about objective, duration of study, age and condition of participants, and collected information (e.g. questionnaires, scales). In addition, the key findings related to mobile and web-based systems were obtained.

Data Synthesis: 62 studies were included encompassing 13,338 participants. A total of 50 (81%) related to mobile systems, and 12 (19%) related to web-based systems. Technology evidenced favourable effects than pen-and-paper in catastrophizing $(33,30\pm2,99 \textit{ vs } 41,20\pm4,63)$ and disability $(44,77\pm1,69 \textit{ vs } 50,08\pm2,56)$. Technology and

pen-and-paper presented equivalent outcomes in the folowing dimensions of pain: anxiety, depression, interference and pain intensity.

Conclusion: The proposed assessment model based on data fusion combined with a qualitative assessment method revealed to be suitable. Data integration raises several concerns and challenges to the design, development and application of monitoring systems applied to pain.

Keywords: mhealth, pain diaries, pain scales, pain assessment, chronic pain

1 INTRODUCTION

Chronic pain account for billions of dollars in annual medical expenditures [1], loss of quality of life and decreased worker productivity contribute to indirect costs [2–4]. As persists over a long period of time [5], pain management is widely expensive due to the need of long-term rehabilitation in multi-disciplinary treatments [6]. However, it harder to produce an assessment that leads to the right treatments, so as to avoid inadequately assessed and under-treated [7,8]. Firstly, pain is a highly subjective experience for each individual [9]. Secondly, due to its duration, the assessment is often accomplished at patient's home, that challenges treatment accuracy and cost-effectiveness monitoring. Thus, as self-report is considered the most accurate pain assessment method [10,11], patients should be asked to periodically rate their pain severity and related symptoms. Unsurprisingly therefore, that in the last years, handheld devices and Internet-delivery treatment (IdT) were largely used to chronic pain monitoring. These systems were used for many different purposes [12], namely education, reminders, feedback, and disease control.

The ubiquity of mobile devices and the Internet raised the paradigm of the new care model based more on contacts than on visits [13]. In fact, the ability to interact with the system anywhere and at anytime thoroughly changes the coordinates of time and place and offers invaluable opportunities to the healthcare delivery. Moreover, mobile devices showed significantly advances in storage capacity, battery efficiency, portability [14] and ability to access internet-based resources [15], that increased its suitability to healthcare systems. The adoption of technology allowed the development of electronic pain diaries (ED) as

computerised version of paper pain diaries (PD). These systems enable patients either to report complaints close in time that pain occurs, called ecological momentary assessment (EMA), or to address retrospective pain, that consists in pain recall over some period of time. Instead an isolated value, pain results from multiple aspects [16–20], such as sensory (e.g. location, intensity), affective (e.g. depression, anxiety) and cognitive (e.g. quality of life). For this reason, chronic pain patients are called to answer many questionnaires and scores and/or to adopt specific behaviours as a way to treat their pain in all its dimensions. For example, the monitoring program may include self-monitoring of pain, adherence to prescribed medications, regular exercise, and weight control. In summary then, the monitoring of chronic pain patients leads to many challenges across a range of topics such as technology (e.g. to collect and send data), clinical settings (e.g. duration of treatment, momentary pain or recall pain), and multi-dimensional pain assessment (e.g. questionnaires, scales).

The aims of this study were to describe mobile and web-based systems applied to chronic pain monitoring, and to suggest an assessment methodology based on statistical analysis, to determine the benefits obtained from adopting these technologies.

2 METHODS

2.1 Research Questions

The primary questions of this review were (RQ1) which mobile and web-based systems have been used in the monitoring of chronic pain patients? (RQ2) Which data (e.g. questionnaires and scales) have been obtained in these systems? (RQ3) How patients' data are collected and transmitted to the physicians? (RQ4) What is the effect of these systems in patient self-reporting across different dimensions of pain? (RQ5) Is there any mathematical proven method that sustains the conclusions?

2.2 Inclusion and Exclusion Criteria

Studies were included in this review if they met the following criteria: (1) constituted computerised systems related to chronic pain complaints, (2) included data about pain assessment and (3) were achieved via mobile devices (e.g. smartphone, PDA, tablet PC) or

web-based forms, (4) preliminary or definitive results were presented, and (5) were written in English. These criteria were also applied to studies obtained from reference tracking. Reviews, study protocols, and studies where data acquisition relied exclusively on e-mails or chats were excluded. There were no age or disease restrictions: participants could be either adults or children, might comprise chronic pain patients or healthy individuals with pain complaints.

2.3 Search Strategy

The team conducted a systematic search in the following electronic databases: BioMed Central, Pubmed Central, and ScienceDirect. Only the studies published from 2000 up until 30th June 2012 meeting the inclusion criteria were considered to this study. The last search was run on 9th July 2012. Appendix I contains details of the electronic search. Every study was independently evaluated by two reviewers (NP and PA) and its suitability determined with the agreement of both parties. A third reviewer (JV) was considered to adjudicate on differences of opinion but was not required because a consensus was reached. The studies were also examined to identify and isolate clusters reporting the same data, so as to avoid the risk of bias [21].

2.4 Extraction of Study Characteristics

The data extracted from the studies, were tabulated (see Table II) and grouped into mobile and web-based systems. Every study was detailed with year of publication, main objective, healthcare condition, duration of the study, age of studied population (median and standard deviation (SD)), number of participants, data inserted directly into the system and the complementary data that support it, whose completion occurs external to the system (e.g. paper questionnaire, phone interview). The data managed by the system were grouped into three categories: pre-treatment (data obtained during the recruitment of participants were excluded), treatment and post-treatment (also includes follow up). However, data related to intervention quality and satisfaction assessment were omitted from this review. The key findings related to mobile and web-based systems are shown in Table I. Finally, meta-analysis included studies comprising randomised controlled trials (RCTs) that evaluate the usage of ED or IdTs and presented pre and post-treatment comparisons. A mathematical model was used (see section 2.7.1) to determine the effect of technology in the monitoring of pain. Firstly, the pain

outcomes obtained in the RCTs' groups (intervention and control) were converted to a 0–100 scale. Secondly, a qualitative assessment (see section 2.7.2) was computed to build an oriented analysis according different dimensions of pain, namely: anxiety, catastrophizing, depression, disability, interference and pain intensity.

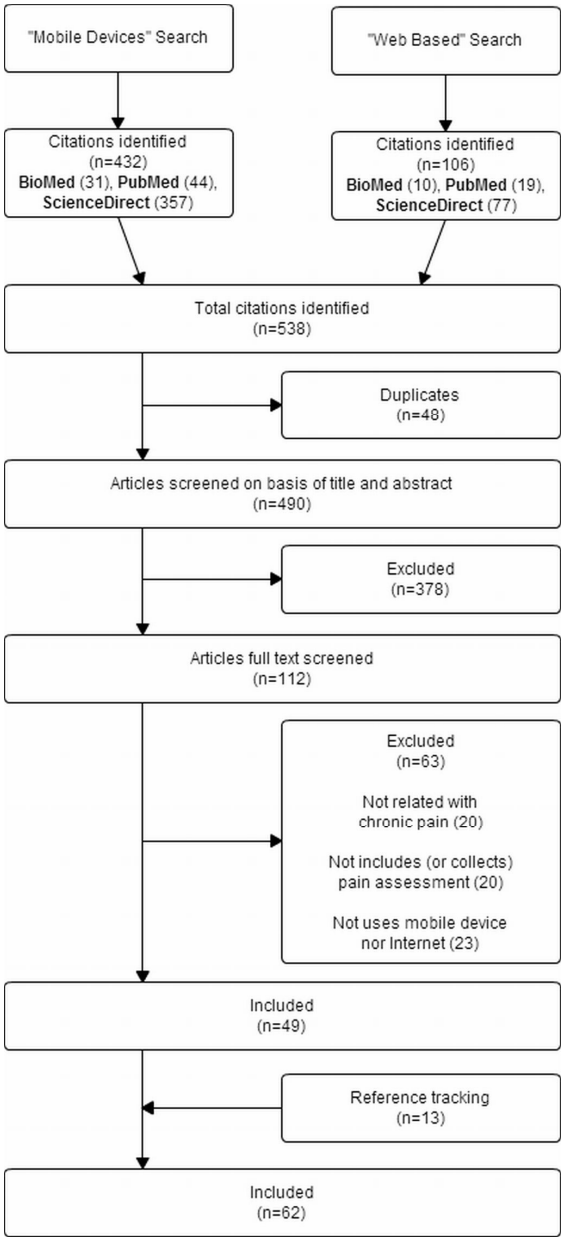

Figure 1: Selected Studies

2.5 Quality Assessment

The methodological quality of all studies was independently assessed by two reviewers (NP and PA) using a list of 10 criteria, which was formulated for the purpose of this study (see Appendix II). Each criterion was rated as either poor/absence (=0), reasonable (=1) or good (=2). Items scores were summed to obtain a total study quality score (range 0-20). As shown in Table II, the quality sum scores were divided into studies with above or below average quality.

2.6 Risk of Bias Assessment

Two reviewers (NP and PA) independently assessed the risk of bias of each RCT included in meta-analysis (see Appendix III) using the Cochrane Collaboration's risk of bias tool [22]. Distinct domains were evaluated such as: method used to generate and to conceal the allocation sequence, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.

2.7 Mathematical Analysis

2.7.1. Statistical Data Fusion

The mathematical model is based on the data fusion methods described in [23–25] and summarized below.

Let us consider n sets of data samples each of which has a Gaussian distribution $N(\bar{x}_i, \sigma_i)$, where $\bar{x}_i$ and σ_i are respectively the mean (or mathematical expectation) and the standard deviation of samples in set i. Then, the probability distribution of the aggregated set is Gaussian with mean $\bar{x}_i$ and standard deviation σ computed as:

$$\bar{x} = \sum_{i=1}^{n} a_i x_i = \alpha \sum_{i=1}^{n} \frac{x_i}{\sigma_i^2}$$

where a_i is defined by

$$a_i = \frac{1}{\sigma_i^2} \alpha, \; i = 1, \ldots, n$$

$$\alpha = \left(\frac{1}{\sigma_1^2} + \frac{1}{\sigma_2^2} + \ldots + \frac{1}{\sigma_N^2} \right)^{-1}$$

$$\sigma^2 = \sum_{i=1}^{N} a_i^2 \sigma_i^2$$

The mean and the standard deviation so computed are used for the qualitative analysis method that we proposed in the next section (2.7.2).

2.7.2. Qualitative Analysis

Let us consider:

σ_T: standard deviation of technology outcome;

σ_P: standard deviation of pen-and-paper outcome;

$\bar{x}_T$: mathematical expectation of technology outcome;

$\bar{x}_P$: mathematical expectation of pen-and-paper outcome;

Consider furthermore the following conditions:

Condition (P): $\bar{x}_P \in \left[\bar{x}_T - \sigma_T, \bar{x}_T + \sigma_T \right]$ or $\bar{x}_T \in \left[\bar{x}_P - \sigma_P, \bar{x}_P + \sigma_P \right]$ for instance as shown in Figure 2 where $\bar{x}_T = 3, \bar{x}_P = 2, \sigma_T = 1.2, \sigma_P = 0.6$

The opposite condition is pictured in Figure 3 with $\bar{x}_T = 3, \bar{x}_P = 1, \sigma_T = 0.9, \sigma_P = 0.8$.

The rational of condition (P) is that since the standard deviation σ is the average magnitude of the sample dispersion with respect to its mean value $\bar{x}$ (mathematical expectation), any value x that is located at a distance from $\bar{x}$ less than the standard deviation (that is, $|x - \bar{x}| < \sigma$) may be considered as *qualitatively* equal to $\bar{x}$.

From condition (P) described above, a qualitative analysis is performed to know which one among *technology* and *pen-and-paper* provides the best way to get fair results in pain monitoring.

CASE 1: when the lower mean value (mathematical expectation) implies better results:

If condition (P) is verified, then using technology or pen-and-paper gives rise to the same conclusion, even though the mean values may be different;

else if $(\bar{x}_T < \bar{x}_P)$

then technology provides better results than pen-and-paper;

else pen-and-paper provides better results than technology.

CASE 2: when the higher mean value (mathematical expectation) implies better results:

If condition (P) is verified, then using technology or pen-and-paper gives rise to the same conclusion, even though the mean values may be different;

else if $(\bar{x}_T > \bar{x}_P)$

then technology provides better results than pen-and-paper;

else pen-and-paper provides better results than technology.

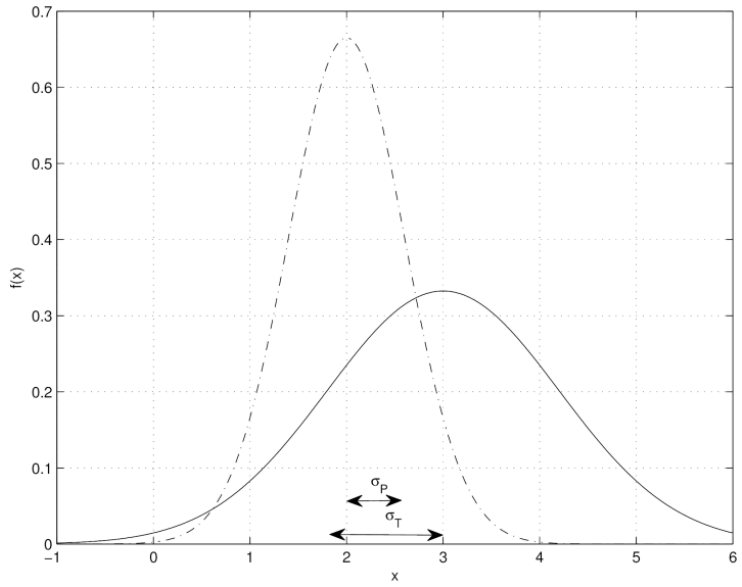

Figure 2: Technology and pen-and-paper are qualitatively equivalent

$$(\bar{x}_T = 3, \bar{x}_P = 2, \sigma_T = 1.2, \sigma_P = 0.6, \bar{x}_P \in \left[\bar{x}_T - \sigma_T, \bar{x}_T + \sigma_T \right])$$

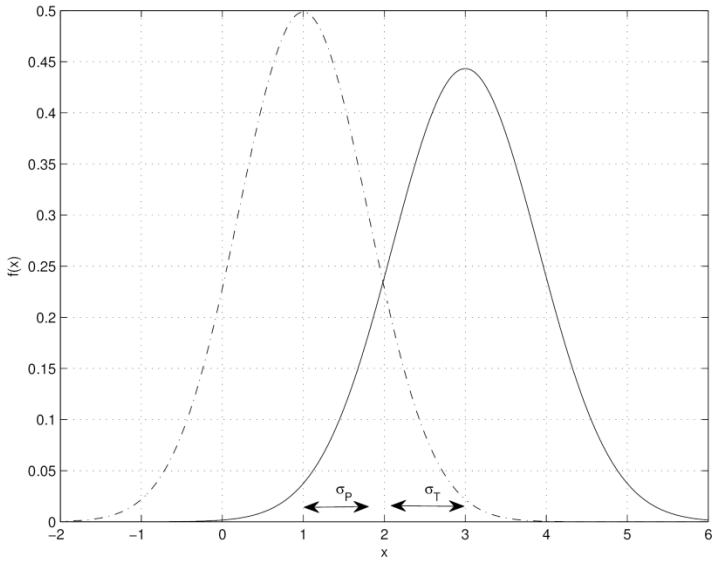

Figure 3: Technology and pen-and-paper are qualitatively different

$$(\bar{x}_T = 3, \bar{x}_P = 1, \sigma_T = 0.9, \sigma_P = 0.8, \bar{x}_P \notin \left[\bar{x}_T - \sigma_T, \bar{x}_T + \sigma_T \right], \bar{x}_T \notin \left[\bar{x}_P - \sigma_P, \bar{x}_P + \sigma_P \right])$$

2.7.3. Considerations for the Analysis

Several studies were excluded from this analysis due to the absence of comparison between pre-treatment and post-treatment outcomes [26–33], or absence of technology validation purpose [34]. The remaining sixteen unique studies were assessed in terms of risk of bias (see Appendix III). Three studies appraised to be at lowest risk of bias were that by [35–37] which met every criterion except the blinding of participants, personnel and outcome assessors. In fact, none of the included RCTs met this criterion. The lack of information and explanation for attrition and missing data was observed, whereas all studies clearly reported the different outcomes. These outcomes, that represent distinct dimensions of the pain, were used to implement statistical analysis across the included RCTs. During the analysis process one study was excluded due to the inexistent of SD in the reported data [38]. In addition, several studies were partially excluded due to high SD in some outcomes (a.k.a. outlier) [39,40], or due to unfeasible conversion from t-scores to continuous scale [35]. Instead of an individually analysis of the studies, the pre and post-treatment data, obtained from IG and CG across the different RCTs, were combined using data fusion methods [23–25] and compared so as to produce a more accurate conclusion. Thus, as shown in Table III, the adoption of technology was assessed not only related to pain intensity, but also to physical and cognitive outcomes such as anxiety, catastrophizing, depression, disability and interference. This dimension was divided into two sections, one of which regards the outcomes when the lower value means less interference (see Interference - I) and the other, when the higher value represents less interference (see Interference - II).

3 RESULTS

As illustrated in Figure 1, our review identified 490 unique citations, of which 378 were excluded as a result of screening, in terms of title, abstract, and keywords. Full text evaluation of the remaining 112 papers resulted in the exclusion of 63 papers that did not match the defined criteria. In addition, the reference tracking allowed for the inclusion of 13 additional papers. In summary then, our review examined 62 papers, representing 55 unique studies, due to the fact that studies reported the same data were clustered to avoid risk of bias.

The included studies encompass a total of 13,338 participants distributed by 43 studies (78%) related to mobile systems and 12 (22%) studies highlighted web-based systems. Moreover, 16 of the 55 studies (29%) included in this review were published before or during 2006, and of the remaining 39 studies, 27 studies were published between the beginning of 2008 and the end of 2010. The quality rating of 25 studies (45%) was lower than the mean and that of 30 was higher (55%). Thirty-two studies (58%) included complementary data, obtained outside the system in at least one of the following phases: pre-treatment (28 studies), treatment (8 studies) or post-treatment (16 studies).

The most representative objective was the validity of IdT (12 studies, 22%), the assessment of ED (12 studies), the comparison between ED and PD (nine studies), comparison between recalled pain and EMA (six studies), and the evaluation of medication in treatment of patients suffering from pain (three studies). Eight studies reported the correlation with the pain, namely: physical activity, relationship, emotional distress, fear, and sleep.

The cognitive-behavioural therapy (CBT) was presented in 19 studies, of which seven were related to mobile systems. The remaining 12 studies presented CBT as support of IdT, and included tailored exercises according to participants' symptoms, multimedia content, information and lessons about physical, cognitive, behavioural and motivational topics. The main principles of CBT for chronic pain management are based on helping the patient to understand how pain experience, coping-skills training, and cognitive restructuring are affected by the cognition and behaviour [41]. Potentialities and risks related to ED, PD and IdT mentioned in the included studies were tabulated as shown in Table I. It is highlighted that use of ED may solve the lack of reliable data, because patients tend to use it more often than a PD and thus retrospective completion is prevented. Moreover, ED and IdT may lead to effective communication between providers and patients, which is essential to a comprehensive pain assessment and treatment strategy. Firstly, providers may decide earlier and more accurately due to real-time analysis capability. Secondly, it may positively influence patients' behaviours and well-being as consequence of sense of closeness with healthcare personnel, and thus improve satisfaction with care, medication adherence, recall and comprehending of medical information, functional and physiological status [42–45]. Since the data are collected through

ED or IdT its integration may be automated, resulting in time-saving and cost-efficaciousness. The IdT revealed its suitability for long-term monitoring. However, difficulty with handling the ED and IdT that may lead to missing values and to increase the time required to fill data, communication problems and inefficient use of collected data to improve treatments, were all limitations that were detected.

Table I: Key findings obtained from included studies

Key Findings
Potential
ED may produce more accurate momentary state measures since the moment of the recording is determined (e.g. several times during the day or in specific moments according with patients' activities)
ED may produce more reliable information, because the patients tend to use it more often than a PD
ED may avoid hoarding (retrospective fill in diary at one time)
IdT may produce positive changes in health status for long periods of time (e.g. at 3/6/12 months follow up)
IdT are cost-efficaciousness (e.g. data integration, low cost communication, redution of clinical visists, educational content delivery related to pain conditions)
ED and IdT are a time-saving method for obtaining data (e.g. automated data integration)
ED and IdT may provice physicians with real time analysis (e.g. early detection of changes in pain parameters, clinical reports on the fly)
ED and IdT may cause positive effect in patients since they feel that healhcare personnel are closely and monitoring their progress
Risks
ED assessment use may lead to difficulties in handling the apparatous for some people
ED may produce high numbers of missing values (e.g. dropouts, attrition, malfuntion or need to replace devices)
ED and IdT may required time consuming in understand and handling the system
ED and IdT may increase the time required to completition of questionnaires and/or slowness in the wireless transferrel of data may occur
Lack or even absence of collected data incorporation in the treatment
Success of the ED and IdT depends of the commitment of patients on it

3.1 Mobile Systems

Forty-three studies were related to mobile systems, of which 35 (81%) were designed to allow its usage in patient home, at least during one phase of the intervention (pre/post-treatment, treatment). The remaining eight studies, limited its use to hospital facilities during the patients' visits and thereby only comparisons among sporadic records collected during the treatment period were provided. Meanwhile, 19 studies presented data transmission to a remote server

immediately after its edition. Three studies did not report this process, whereas 21 studies reported elapsed time between the editing and the subsequent sending. Thus, data were collected at intervals or in the clinic visit or at the end of the study. Internet was the preferred channel for sending data (14 studies), followed by uploading through personal computer (9 studies) and SMS (3 studies). Data transmission after its edition may allow real-time access to physicians, and therefore, clinical decisions supported with updated information according to patient conditions. Moreover, it may provide the enforcement of trigger messages and alerts according to the obtained values. This method was highlighted by four studies and comprised a clinical session report generation, SMS alerts according to answers and warning messages deriving to activity patterns, displayed in PDA. The data storage in a Personal Health Record (PHR), wrist actigraphy used in sleep assessment and activity monitoring supported by a Body Area Network (BAN) were proposed in one study each. Interactive voice recorded (IVR) was referred in two studies [46,47]. Time of intervention ranged from one clinical session to 52 weeks (one year).

3.2 Web-based Systems

Web-based systems were reported in 12 studies, of which 11 consisted in RCTs, comprised by two groups of participants called: intervention group (IG) and control group (CG). The difference between them is that a web site was used to deliver the treatment to IG participants. At the end of intervention, participants of both groups were assessed and the IdT effects were determined. The IdT consisted with online questionnaires and/or CBT. All the articles reported positive effects and improvement in health status. With the exception of [37,39], all web-based systems used emails or phone calls jointly with Internet (83%). Six studies adopted emails [48–53] and three of them also performed phone calls [51–53], so as to remind patients to use and/or interact with the system. In addition, emails were applied to obtain data [40,50–52], to support the system handling [36,49], and together with phone calls, were administered to establish contact between healthcare professionals and patients [36,54]. One study [40], allowed phone calls to support the system handling. Finally, [55] used SMS to remind patients to collect data. In the same study, mobile phones with Internet access were used to present a

web site whereupon treatment was provided, and therefore, it has been classified as web-based system. Time of intervention ranged from 3 to 52 weeks (one year). It should be noted that remote data transmission is not require in these systems, as occurs in mobile monitoring applications.

Table II: Studies characteristics

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
Mobile systems									
Allen [56,57], 2009	To compare recalled average pain, assessed at the end of the day, with the average of real-time pain ratings recorded throughout the day	Osteoarthritis	1 weekday and 1 weekend day	157 (61.7 ± 10.6)	Yes	**Pre:** CSQ	Pain intensity (VAS), immediately after waking, then approximately every 2 hours throughout the day (in order to complete at least 7 pain ratings per day) and immediately before going to sleep (to recall the average pain during the day)	NR	L
Anatchkova [58], 2009	To assess a prototype computerised adaptive test of chronic pain	Chronic pain	1 session	100	No		Pain intensity (NRS), computer adaptive dynamic assessment of The Chronic Pain Impact Item Bank [59], and SF-12, in the medical appointment	NR	L
Axen [60,61], 2011	To evaluate the method of collecting frequent data using mobile phones and text messages	Low back pain	6 months	262 (44)	Yes	**Pre:** Pain intensity (NRS), location, duration and frequency, self-rated general health (5-point Likert scale). EuroQoL 5 (EQ5D) **Post:** EQ5D and self-rated general health (6-months follow up)	Pain intensity (NRS), once a week using SMS	Instant	L
Badr [62], 2010	To determine the daily impact of patients with pain on spousal relationships	Chronic cancer pain	14 days	54 patients (49.4 ± 10.8) 48 partners (51.3 ± 11.5)	Yes		**Patients:** pain intensity (NRS), mood, medication taken and pain relief, 6 times per day between 9am and 9pm. Perceptions of relationship functioning in the last assessment of the day. **Partners:** patients' pain, own mood and perceptions of relationship functioning, at similar time points	Instant	L
Baron-Mahn- [63,64], 2009	To compare sensory abnormalities in patients with different neuropathic pain syndromes	Neuropathic pain	1 session	2094 painful radiculopathy (59.4 ± 14.4) 1623 painful diabetic neuropathy (61.9 ± 13.0)	No		MOS-SS, PHQ, PD-Q and pain location (pinpointed in 3D mannequin) in the medical appointment	Delayed	L

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
				498 postherpetic neuralgia (60.6 ± 15.4)					
Broderick-Schneider [46,65,66], 2008	To examine the accuracy of ratings for reporting periods ranging from 1 day to 28 days related to pain and fatigue measures	Fibromyalgia and osteoarthritis and rheumatoid arthritis	1 month	83 (56.2 ± 11.1)	Yes	**Treatment:** 10 random recalls pain assessment via phone interview (interactive voice recording was used) **Post:** Pain Intensity (VAS)	SF-36, BPI, BFI, MPQ, 7 times per day during the patients' waking hours	Delayed	L
Clauw [34], 2008	To evaluate the efficacy and tolerability of milnacipran in treating the multiple domains of fibromyalgia	Fibromyalgia	15 weeks	399 IG 100 mg/d (49.5 ± 10.9) 396 IG 200 mg/d (50.4 ± 10.6) 401 CG (50.7 ± 10.4)	Yes	**Pre:** FIQ, MASQ, MOS-SS, MDHAQ, MFI, BDI, and ASEX **Treatment:** 3, 7, 11 and 15 week visit: PGIC, SF-36, FIQ, MASQ, MOS-SS, MDHAQ, MFI. BDI and ASEX only at week 15	**Diary:** pain intensity (VAS), 5 times per day (morning, 3 during day and evening) **Weekly:** pain, fatigue, influence of pain in self-care (VAS)	Instant	H
Connelly [67], 2010	To evaluate how parent responses to their child's pain predict daily adjustment of children	Juvenile idiopathic arthritis	14 days	9 (12.3 ± 3.4)	Yes		**Children:** pain intensity (VAS), PANAS-C, CALQ, 3 times per day (morning, afternoon, and evening) **Parents:** PANAS, ARCS at the same time points, using a separate PDA	Delayed	L
Gaertner [68], 2004	To compare pain records made between electronic diaries and self-report paper diaries	Chronic cancer and non-cancer pain	4 weeks	24 (49.9 ± 15.1) Crossover randomized between IG and CG	Yes		Pain intensity (NRS), once a day and symptom assessment (fatigue, nausea, dyspnea, weakness,…), once a week	Delayed	L
Ghinea [69], 2008	To evaluate the usage of electronic pain diaries using 3D-Pain drawings	Low back pain	5 days	45 (46.1)	Yes		Pain intensity (VAS) and location (pinpointed in 3D mannequin), 3 times a day	Instant	L
Giske [70], 2010	To compare daily and weekly recalled pain over time and their correspondence with	Musculoskeletal pain	5 days	50 (50.0 ± 11.0)	Yes	**Pre:** HSCL-25, FIQ **Post:** Pain intensity (VAS) and pain location	Pain intensity (NRS), 5 times a day between 9am and 9pm, using SMS	Instant	L

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
	pain intensity								
Heiberg [71], 2007	To compare the usability and accuracy between electronic diaries and self-report paper diaries	Rheumatoid arthritis	2 periods of 3 weeks	38 (58.4 ± 12.9)	Yes		**Diary:** pain intensity (VAS), fatigue, and patient global evaluation of their disease, RADAI, 4 times per day **Weekly:** MHAQ, SF-36	Instant	H
Jamison [28], 2001	To compare pain records made between electronic diaries and self-report paper diaries	Low back pain	1 year	20 IG (42.1 ± 5.0) 16 CG (43.3 ± 9.2)	Yes	**Pre:** CPEQ, SCL-90 **Treatment:** MPQ-SF (once a month). Pain reported weekly by phone interview **Post:** SCL-90	Pain intensity (VAS) and pain ratings of the previous 16 waking hours, once a day (bedtime)	Delayed	H
Jamison [72], 2002	To determine whether patient input via electronic VAS is equivalent to input via pen-and-paper VAS	Healthy volunteers	1 session	24 (34.4)	No		Pain intensity (VAS)	Delayed	L
Jamison [73], 2006	To compare momentary pain intensity ratings on an VAS with weekly recalled pain	Low back pain	1 year	21 (42.0 ± 4.9)	Yes	**Pre:** CPEQ, SF-36, MPQ-SF, SCL-90 **Treatment:** Pain reported weekly by phone interview	Pain intensity (VAS), at least once a day	Delayed	H
Jamison-Wasan [26,27], 2010	To determine whether CBT improves overall compliance with opioids prescribed for noncancer pain patients	Chronic back or neck pain	6 sessions	21 IG ED+CBT (47.0 ± 7.8) 21 CG #1 ED (46.6 ± 6.8) 20 CG #2 ED (49.6 ± 6.8)	Yes	**Pre and Post:** ABC, BPI, COMM, HADS, MINI, PDI, SOAPP-R **Post:** PDUQ	BPI , pain location once a month at clinic visit Wasan's study, also includes four questions to assess craving for prescription opioids over the past 24 hours (14 days ED at patients' home) **CBT:** Group educational sessions (e.g. opioid addiction risks and medication compliance, making lifestyle changes, ...) and individual motivational counseling (review of medication adherence, support for patients' efforts, education on pain management and drug misuse, ...)	Delayed	H
Jespersen [74], 2012	To determine the correlation between low back pain and	Low back pain	1 year	188 (44.4 ± 9.0)	Yes	**Pre:** AMS	AMS, IPAQ, once a week using SMS	Instant	H

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
	leisure time physical activity								
Koroschetz [75], 2011	To compare patients with painful diabetic neuropathy and fibromyalgia	Fibromyalgia and neuropathic pain	1 session	1623 painful diabetic neuropathy (61.9 ± 13.0) 1434 fibromyalgia (51.9 ± 10.8)	No		MOS-SS, PHQ, PD-Q and pain location (pinpointed in 3D mannequin) in the medical appointment	Delayed	L
Kvien [76], 2005	To compare the usability and accuracy between electronic diaries and self-report paper diaries	Rheumatoid arthritis	2 sessions	30 (61.6)	No		Pain intensity (VAS), fatigue, and patient global evaluation of their disease, RADAI, MHAQ, SF-36, at 2 medical appointments	Instant	L
Lewandowski [77], 2010	To compare daily associations between sleep and pain in adolescents with chronic pain and healthy adolescents	Chronic pain and healthy participants	10 days	39 chronic pain (15.3 ± 1.5) 58 healthy participants (14.7 ± 1.8)	Yes	**Pre:** CES-D	Sleep quality (NRS) in the morning and pain intensity (NRS) in the evening. Integrated with wrist actigraphy to monitorize the sleep	Delayed	L
Levin [78], 2006	To evaluate spoken dialogue methodology for real-time data collection from patients	Healthy volunteers	2 weeks	24	Yes		Pain intensity (NRS), location, duration reported via automated speech telephony delivery (a.k.a automated speech recognition)	Instant	L
Li [79], 2010	To evaluate the safety and efficacy of a naturally derived topical oil, for the treatment of neuropathic pain	Neuropathic pain	2 sessions separated by 1 week	60 (69.0 ± 10.0)	Yes	**Pre and Post:** MPQ-SF	MPQ-SF, 8 times per day (hourly between 2 and 9 pm)	Delayed	H
Lind [80], 2008	To evaluate palliative home care patients' experiences of assessing their pain by using a pain diary together with digital	Palliative care	Until 17 days	12 (67.5 ± 7.8)	Yes		Pain intensity (VAS), 3 times a day (8am, 1pm, 8pm)	Instant	L

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
	pen and Internet								
Litt [47], 2009	To determine whether CBT operates by effecting changes (cognitions, affects,...) in the context of painful episodes.	Neuropathic pain, odontogenic pain	7 days pre + 14 days post	32 IG 22 CG Overall (41.0 ± 11.9)	Yes	**Pre and Post:** MPI, CES-D	Pan location, unpleasantness experienced, perceived control over pain, catastrophization and coping, 4 times per day (from 8am to 10pm). Interactive voice recording was used **CBT:** relaxation training, cognitive restructuring and stress management	Instant	H
Luckmann [81], 2010	To compare the usability and accuracy of a electronic pain diary with a paper pain diary	Chronic pain	NR	4	Yes		Pain intensity (NRS), location, activity and treatment completed each 2-4 waking hours. Acute pain registered when happens. Sleep report in the morning and end of day report before sleep. Data integration with PHR	Instant	L
Marceau [82], 2010	To examine barriers to the use of electronic pain diaries and compare them with paper diaries	Chronic pain	10 sessions	67 IG (48.5 ± 11.6) 67 CG (50.5 ± 11.0)	No		BPI at each monthly clinic visit. Pre and post-treatment and 5-month follow up: BPI, PCS, ODI, CES-D	Instant	H
McClellan [29], 2009	To evaluate use of a handheld electronic wireless device to implement a pain management protocol	Sickle cell disease	8 weeks	9 IG 10 CG Overall (13.4 ± 2.9)	Yes		Pain intensity at morning and evening (10-point Likert scale), pain location, sleep quality, and functional limitations once a day **CBT:** coping skills program, once a day. Parents presence is allowed	Instant	H
Oerlemans [38], 2011	Personal digital assistant on self-management of irritable bowel syndrome patients	Recurrent abdominal pain	4 weeks	37 IG (35.9 ± 11.7) 39 CG (40.6 ± 15.5)	Yes	**Pre and Post (upon treatment and 3-month follow up):** Pain intensity (5-point Likert scale), CFSBD, IBS-QoL, PCS	Pain intensity (5-point Likert scale) 3 times per day (morning, afternoon and evening). Sleep quality and intended activities for the day. (morning), accomplished activities, cognitions, and feelings (afternoon), and satisfaction with activity level and achievements of that day (evening) **CBT:** situational feedback on their	Instant	H

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
							diaries from a psychologist		
Okifuji [83], 2011	To determine temporal co-variations among pain, fatigue, and emotional distress in people with fibromyalgia syndrome	Fibromyalgia	30 days	81 (28.8 ± 6.2)	Yes		Overall pain (7-point Likert scale), fatigue, head pain, emotional distress, abdominal pain, sense of relaxation, muscle pain, and sense of swelling, 3 times per day (morning, early afternoon, late afternoon)	Delayed	L
Page [84], 2010	To assess the feasibility of acquiring real-time pain data in a clinical setting	Parkinson's chronic pain	1 session	14 (65.1)	No	**Pre:** PDQ-39, BDI-II, UPDRS	MPQ, in the medical appointment	Delayed	L
Palermo [33], 2004	To compare the usability and accuracy of a electronic pain diary with a paper pain diary in children	Recurrent headache, idiopathic arthritis	7 days	30 IG (12.3 ± 2.4) 30 CG (12.3 ± 3.0)	Yes	**Pre:** CALI	Pain intensity (Faces pain scale [85]), pain symptoms (occurrence, location, duration, and emotional upset), CSI, and CALI, once a day	Delayed	H
Peters [86], 2000	To examine temporal characteristics of pain intensity in patients differing in duration of pain	Chronic pain	4 weeks	80 (40.6 ± 6.7)	Yes	**Pre:** MPI, SF-36, BSI **Post:** CSQ (6 months follow up)	Pain intensity (7-point scale) and signal controlled diary (items: pain cognition, pain coping, sleep quality, ...), 4 times per day between 8am and 9:30pm	Delayed	H
Roelofs [87], 2004	To examine the relationships between pain-related fear, attention to pain, and pain intensity in daily life	Low back pain	At least 7 days	40 (46.4 ± 9.9)	Yes	**Pre:** TSK, QBPDS	Pain intensity (PVAQ), TSK, 8 times per day between 8am (weekend 9am) and 10pm.	Delayed	L
Schurman [35], 2010	To examine whether adding biofeedback-assisted relaxation training results in better clinical outcomes	Recurrent abdominal pain	6 weeks	10 IG 10 CG Overall (12.2 ± 2.8)	Yes	**Pre and Post:** BASC, PedsQL, completed by children and parents	Pain intensity (Faces pain scale Revised), once per day (bedtime) **CBT:** relaxation sessions, such as abdominal breathing, progressive muscle relaxation, imagery, and autogenic hand-warming. Multimedia content for home practice	Delayed	H
Sorbi [88], 2007	To evaluate the support home-based training of behavioural attack prevention in	Recurrent migraine	4 weeks	5	Yes		Pain intensity (VAS). 1st test run: 4-5 times per day. 2nd test run: 2-3 times per day	Instant	L

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
	chronic migraine						**CBT:** migraine headache, medication use, attack precursors, self relaxation and other preventive behaviour		
Stinson [89], 2008	To evaluate the construct validity and feasibility of a electronic pain diary	Juvenile idiopathic arthritis	Study 1: 2 weeks Study 2: 1 week pre+2 weeks post	Study 1 76 (13.4 ± 2.5) Study 2 36 (12.6 ± 2.4)	Yes	**Post:** PedsQL, PCQ	Pain intensity, pain unpleasantness, pain's interference with aspects of quality of life and other symptoms (e.g. stiffness and fatigue) (VAS), 3 times per day (upon waking, after school, and before bed)	Instant	H
Stinson [90], 2012	To determine and evaluate a computerised pain assessment tool for use in pediatric rheumatology	Rheumatoid arthritis	1 session	24 children (5.9 ± 0.9) 77 youth (13.5 ± 3.1)	No		Pain intensity: faces pain scale (children), NRS (youth), in the medical appointment	Instant	H
Stone [31], 2003	To compare pain records made between electronic diaries and self-report paper diaries	Chronic pain	21 days	40 IG (43.0 ± 9.0) 40 CG (48.0 ± 10.8)	Yes	**Pre:** MPQ-SF	BPI, PD-IIP, HAQ, 3 times per day (10pm, 4am, 8am)	Delayed	H
Stone-Kelly [30,32], 2003	To compare momentary pain intensity ratings on an VAS (collected with different density) with weekly recalled pain + To examine the within-person relationships between pain intensity, sensory characteristics, affective qualities, and activities limited by pain	Chronic pain	2 weeks	22 IG 3 prompts/day (49.0 ± 10.7) 22 IG 6 prompts/day (53.5 ± 10.4) 24 IG 12 prompts/day (50.3 ± 10.3) 23 CG (49.8 ± 12.5)	Yes	**Pre:** Questionnaire to assess anxiety, stress, pain, health, and quality of life **Pre/Treatment:** Questionnaire, once a week, to assess pain and mood, the momentary and the occurred over the last 7 days **Treatment:** Questionnaire once a week to assess interference of ED with participants' daily routines	Pain intensity (VAS), and other questions related to sensory, affective and physical aspects, 3, 6 or 12 times a day. Kelly's study includes all the IGs	Delayed	H
Turner [91], 2005	To evaluate, via electronic diaries, the short-term efficacy of	Chronic pain	8 weeks	61 IG (39.3 ± 11.1)	Yes	**Pre:** GCPS	Pain intensity (NRS), pain-related activity interference, jaw use limitations, and several questions	Delayed	H

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
	a CBT as compared with an education/ attention control condition.			65 CG (35.4 ± 10.5)			adapted from CSQ, SOPA, PCS, and DCI, 3 times per day (morning, afternoon, and evening) **CBT:** At each session activity goals were recommended (correct jaw posture, progressive relaxation practice, breathing exercises, physical exercise, ...)		
Wallasch [92], 2012	To validate an algorithm for assigning patients to headache treatment program	Recurrent headache	4 weeks	545 (43.1 ± 12.9)	Yes		MIDAS, GCPS, HADS, SF-12	Delayed	L
Weering [93], 2012	To examine whether patients responded to personalized messages by changes in activity patterns	Low back pain	2 weeks	16 (40.7 ± 13.8).	Yes	**Pre:** RMDQ, SoC	Pain intensity (VAS), 3 times a day (noon, 4pm, 8pm). Integration with Body Area Network (BAN)	Instant	L
Younger [94], 2009	To examine the effectiveness of low-dose naltrexone in treating the symptoms of fibromyalgia	Fibromyalgia	14 weeks	10 (46.5 ± 10.3)	Yes	**Treatment:** FIQ every 2 weeks	Fibromyalgia severity, average pain intensity, highest pain, and other symptoms (fatigue, sadness, stress, sleep quality, ability to think and remember, …), once a day (night)	NR	L
Web-based systems									
Berman [49], 2009	To evaluate the efficacy of an Internet-delivered treatment	Chronic pain	6 weeks	41 IG (64.3) 37 CG (67.5)		**Pre and Post:** BPI, PSEQ, CED-S, STAI, PAQ, HDM	Pain intensity (BPI), after logon and before logoff in the site **CBT:** abdominal breathing, relaxation, writing about experiences (positives or negatives), creative visual expression and positive thinking. Audio, visual and textual content related to pain		H
Buhrman [36], 2004	To investigate the effects of an Internet-based cognitive behavioural intervention with telephone support	Low back pain	1 week pre+ 1 week post+ 1 week 3-month	22 IG (43.5 ± 10.3) 29 CG (45.0 ± 10.7)		**Pre:** HADS	Pain intensity (VAS), 3 times per day (morning, noon and evening). PAIRS, MPI, CSQ and HADS once a week **CBT:** several modules (pain, stress, physical activities, problem solving,		H

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
			follow up				...) and slideshows and sound files for download		
Devineni [48], 2005	To evaluate the efficacy, time cost-efficiency, and short-term durability outcomes of an Internet-delivered treatment	Recurrent headache	2 weeks pre+ 2 weeks post+ 2 weeks at 2-months follow up	39 IG (43.6 ± 12.0) 47 CG (41.0 ± 11.8)			Frequency, duration, and severity of pain, once a day **Pre/Post/Follow up:** HSQ, CES-D, STAI, HDI **CBT:** muscle relaxation program, and stress coping therapy		H
Hicks [54], 2006	To evaluate the efficacy of an Internet-delivered treatment	Pediatric recurrent paint	2 weeks pre+ 2 weeks post	25 IG (12.1 ± 2.0) 22 CG (11.3 ± 2.2)		**Pre:** PedsQL **Post:** PedsQL (1-month and 3-month follow up)	Pain intensity (NRS), 4 times per day **CBT:** relaxation techniques, lifestyle (diet, exercise), information related to pain		H
Hunt [50], 2009	To assess the Internet-delivered treatment for irritable bowel syndrome	Recurrent abdominal pain	6 weeks	28 IG (39.0 ± 10.0) 26 CG (38.0 ± 12.0)			GSRS-IBS, IBS-QoL, ASI, GAD-Q and CPSQ, conducted at pre-and post-treatment and 3-month follow-up **CBT:** gastrointestinal symptoms and stress and on relaxation training, stress management, catastrophic thinking, exposure therapy and the social consequences of IBS		H
Kristjansdottir [55], 2011	To assess the Internet-delivered treatment	Chronic widespread pain	4 weeks	6 (36.3)		**Pre and Post:** CPAQ, PCS	Pain intensity, interference of pain, planned and achieved activities, feelings, pain-related fear, avoidance, catastrophizing and acceptance, 3 times per day (morning, evening and a time randomly chosen between 11:30 am and 2 pm) **CBT:** feedback SMS with praise, encouragement messages, and exercises		L
Ljótsson [52], 2010	To assess the Internet-delivered treatment for irritable bowel syndrome	Recurrent abdominal pain	10 weeks + 2 weeks at 3-month	42 IG (36.4 ± 10.1) 43 CG		**Treatment:** Gastrointestinal symptom diary	GSRS-IBS, IBS-QoL, VSI, MADRS-S and SDS conducted at pre-and post treatment. 3-month follow up: VSI, IBS-QoL		H

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
			follow up	(32.8 ± 8.6)			and 2 weekly GSRS-IBS **CBT:** mindfulness exercises program, and lifestyle strategies (diet, exercise)		
Lorig [39], 2008	To evaluate the efficacy of an Internet-delivered treatment	Fibromyalgia and osteoarthritis and rheumatoid arthritis	1 year	422 IG (52.2 ± 10.9) 433 CG (52.5 ± 12.2)			Pre and post treatment, and 6/12 months follow up: pain intensity and fatigue (NRS), distress, activities limitations, disabilities and HAQ **CBT:** tailored exercises programmes and medication diaries		H
Palermo [37], 2009	To assess the Internet-delivered treatment	Idiopathic pain	1 week pre + 8-10 weeks post	26 IG (14.3 ± 2.1) 22 CG (15.3 ± 1.8)		**Pre and Post:** RCADS, ARCS	Pain intensity (NRS), CALI **CBT:** two separate websites, one for child access and one for parent access. The child access comprised eight treatment modules (education about chronic pain, recognizing stress and negative emotions, relaxation, distraction, cognitive skills, sleep hygiene and lifestyle, staying active, relapse prevention). Download of multimedia content.		H
Ruehlman [51], 2012	To evaluate an online chronic pain self management program	Chronic pain	14 weeks	162 IG [19..78] 143 CG [19..78]			CES-D, DASS, PCP-S and PCP-EA at pre-treatment, 7-weeks and 14-weeks follow-up **CBT:** several content such as interactive activity, relaxation sessions		H
Strom [40], 2000	To evaluate the effects of applied relaxation and problem solving in the Internet treatment	Recurrent headache	4 weeks pre+ 6 weeks treatment +4 weeks post	20 IG (41.5) 25 CG (39.2)		**Pre:** Pain intensity (VAS), duration, BDI, HDI, MLPC. **Treatment:** Number of times and the total time used for training relaxation. **Post:** Pain intensity (VAS)	**CBT:** several modules concerning relaxation		H
Williams [53], 2010	To assess the Internet-delivered treatment	Fibromyalgia	6 months	59 IG (50.2 ± 12.3)		**Pre:** MINI, PD-IIP	SF-36, BPI, MFI, MOS-SS, CES-D, STPI and PGIC at pre and post-treatment		H

Study/Year	Objective	Condition	Duration	Population Participants (Mean age, SD)	Patient Home	Data			Quality
						As a complement to the system	Collected through the use of system	Transmission	
				59 CG (50.8 ± 10.6)			**CBT:** multimedia content following topics: educational lectures, symptom management and adaptive life style.		

IG: Intervention Group; **CG:** Control Group; **Q:**Quality (**H:** Above average quality **L:** Below average quality); **NR:** Not Reported; **ED:** Electronic Diary; **CBT:** Cognitive-behavioural Therapy

ABC: Addiction Behaviours Checklist [95]; **AMS:** Analysys of Musculoskeletal Symptoms [96]; **ARCS:** Adult Responses to Children's Symptoms Questionnaire [97]; **ASEX:** Arizona Sexual Experience [98]; **ASI:** Anxiety Sensitivity Index [99]; **BASC:** Behaviour Assessment System for Children [100]; **BDI:** Beck Depression Inventory [101]; **BDI-II:** BDI revised; **BFI:** Brief Fatigue Inventory [102]; **BPI:** Brief Pain Inventory [103]; **BSI:** Brief Symptom Inventory [104]; **CALI:** Child Activity Limitations Interview [105]; **CALQ:** Child Activity Limitations Questionnaire [106]; **CES-D:** Center for Epidemiological Studies Depression Scale [107]; **CPAQ:** Chronic Pain Acceptance Questionnaire [108]; **CPEQ:** Comprehensive Pain Evaluation Questionnaire [109]; **CPSQ:** Consequences of Physical Sensations Questionnaire [110]; **COMM:** Current Medication Misuse Measure [111]; **CSI:** Children's Somatisation Inventory [112]; **CSQ:** Coping Strategies Questionnaire [113]; **CSFBD:** Cognitive Scale for Functional Bowel Disorders [114]; **DASS:** Depression Anxiety Stress Scale [115]; **DCI:** Daily Coping Inventory [116]; **EQ5D:** Euro-QoL 5 [117]; **FIQ:** Fibromyalgia Impact Questionnaire [118]; ***G*AD-Q:** Generalized Anxiety Disorder Questionnaire [119]; **GCPS:** Graded Chronic Pain Scale [120]; **GSRS-IBS:** Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome [121]; **IBS-QoL:** Irritable Bowel Syndrome Quality of Life [122]; **IPAQ:** International Physical Activity Questionnaire [123]; **HA*D*S:** Hospital Anxiety and Depression Scale [124]; **HAQ:** Health Assessment Questionnaire [125]**; HDI:** Headache Disability Inventory [126]; **HDM:** Healthy Days Measures [127]; **HSCL-25:** Hopkins Symptom Check List [128]; **HSQ:** Headache Symptom Questionnaire [129]; **MADRS-S:** Montgomery Åsberg Depression Rating Scale-Self report [130]; **MASQ:** Multiple Ability Self-Report Questionnaire [131]; **MDHAQ:** Multidimensional Health Assessment Questionnaire [132]; **MFI:** Multidimensional Fatigue Inventory [133]; **MHAQ:** Modified Health Assessment Questionnaire [134]; **MIDAS:** MIgraine Disability Assessment Score [135]; **MINI:** Mini-International Neuropsychiatric Interview [136]; **MLPC:** Multidimensional Locus of Pain Control [137]; **MOS-SS:** Medical Outcomes Study Sleep Scale [138]; **MPI:** Multidimensional Pain Inventory [139]; **MPQ:** McGill Pain Questionnaire [140]; **MPQ-SF:** MPQ-Short Format; **NRS:** Numeric Rating Scale [141]; **ODI:** Oswestry Disability Index [142]; **PAIRS:** Pain Impairment Rating Scale [143]; **PANAS:** Positive and Negative Affect Schedule [144]; **PANAS-C:** PANAS for Children; **PAQ:** Pain Awareness Questionnaire [49]; **PCP-EA:** Profile of Chronic Pain Extended Assessment [145]; **PCP-S:** Profile of Chronic Pain: Screen [146]; **PCQ:** Pain Coping Questionnaire [147]; **PCS:** Pain Catastrophizing Scale [148]; **PD-IIP:** Personality Disorders Scale of the Inventory of Interpersonal Problems [149]; **PD-Q:** painDETECT questionnaire [150]; **PDI:** Pain Disability Index [151]; **PDQ-39:** Parkinson's Disease Questionnaire-39 [152]; **PDUQ:** Prescription Drug Use Questionnaire [153]; **PedsQL:** Pediatric Quality of Life Inventory [154]; **PGIC:** Patient Global Impression of Change [155]; **PHQ:** Patient Health Questionnaire [156]; **PSEQ:** Pain Self-efficacy Questionnaire [157]; **PV*A*Q:** Pain Vigilance and Awareness Questionnaire [158]; **QBPDS:** Quebec Back Pain Disability Scale [159]; **RADAI:** Rheumatoid Arthritis Disease Activity Index [160]; **RCADS:** Revised Child Anxiety and Depression Scale [161]; **RM*D*Q:** Roland Morris Disability Questionnaire [162]; **SCL-90:** Symptom Checklist-90 [163]; **SDS:** Sheehan Disability Scale [164]; **SF-36:** MOS 36-ltem short-form [165] (SF-12 are a short version of SF-36); **SOAPP-R:** Screener and Opioid Assessment for Pain Patients-Revised [166]; **SoC:** Stage of Change [167]; **SOPA:** Survey of Pain Attitudes [168]; **STAI:** State-Trait Anxiety Inventory [169]; **STPI:** State-Trait Personality Inventory [170]; **TSK:** Tampa Scale for Kinesiophobia [171]; ***U*PDRS:** Unified Parkinson's Disease Rating Scale [172]; **VAS:** Visual Analogue Scale [173]; **VSI:** Visceral Sensitivity Index [174] ***∴***

3.3. Meta-Analysis

The qualitative and quantitative analysis (see section 2.7) revealed that the benefits of technology and pen-and-paper are equivalent in the following dimensions: pain intensity $(48,67 \in [50,98 \pm 3,35] \; and \; 50,98 \in [48,67 \pm 3,49])$, anxiety $(33,68 \in [34,57 \pm 4,09] \; and \; 34,57 \in [33,68 \pm 4,30])$, depression $(4,60 \in [4,77 \pm 0,67] \; and \; 4,77 \in [4,60 \pm 0,70])$ and interference $(75,92 \in [74,09 \pm 3,42], 74,09 \in [75,92 \pm 3,43] \; and \; 37,10 \in [38,11 \pm 3,78], 38,11 \in [37,10 \pm 3,70])$.

On the contrary, is suggested that technology produces better outcomes than pen-and-paper when applied to catastrophizing $((33,30 \pm 2,99) < (41,20 \pm 4,63))$ and disability $((44,77 \pm 1,69) < (50,08 \pm 2,56))$.

Table III: Comparison between pen-and-paper, and mobile and web technology using pre and post treatment results by study and overall

Dimension		Pain intensity												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Berman [49]	BPI (mean)	52	19,4	45,6	18,3	54,3	17,4	47,3	18,4	48,61	13,31	51	12,64	Technology
Buhrman [36]	Pain (mean)	37,4	18,2	34,3	16,8	44,4	14,2	39,6	16,3	35,73	12,34	42,33	10,71	Technology
	MPI - pain severity	63,33331	31,66665	39,99998	18,33333	83,3333	28,33332	53,33331	13,33333	45,86	15,87	58,77	12,06	Technology
Devineni [48]	Headache pain	31,8	17	18,6	13	35,5	15,5	30,6	14,7	23,47	10,33	32,92	10,67	Technology
Hicks [54]	Pain (mean)	48	13	34	24	43	16	47	22	44,82	11,43	44,38	12,94	Pen-and-Paper
Litt [47]	MPI (mean)	43,83332	20,99999	20,49999	16,33333	35,16665	14,33333	24,99999	22,66666	29,29	12,89	32,26	12,11	Technology
Ljótsson [52]	Pain	65	42,5	35	37,5	60	37,5	60	40	48,13	28,12	60	27,36	Technology
Lorig [39]	Pain	65,3	22,7	58,6	24,4	63,7	22,2	63,4	23,1	62,19	16,62	63,56	16,01	Technology
Palermo [37]	Pain	54,5	22,5	35,4	24,2	51,7	16,5	47,6	18,4	45,64	16,48	49,87	12,28	Technology
	Retrospective pain	66,3	18,7	49,6	21,8	61,6	18,4	54,5	20,4	59,22	14,19	58,42	13,66	Pen-and-Paper
Ruehlman [51]	PCP-S - pain severity	76,46875	9,71875	71,09375	12,9375	74,78125	10,90625	71,65625	13,28125	74,53	7,77	73,52	8,43	Pen-and-Paper
Turner [91]	Pain (mean)	43	22	39	24	43	19	40	22	41,17	16,22	41,72	14,38	Technology
Williams [53]	BPI - pain severity	51	14	43	16	49	14	49	15	47,53	10,54	49	10,23	Technology
Fusion	value	**55,90156**	**4,800002**	**40,57251**	**5,081619**	**52,64747**	**4,560069**	**49,01875**	**4,937561**	**48,67**	**3,49**	**50,98**	**3,35**	**Equivalent**
	alpha	23,04002		25,82285		20,79423		24,37951						

Dimension		Anxiety												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Berman [49]	STAI	48,08326	17,58331	45,41659	19,87497	43,37493	14,70831	47,16659	16,16664	46,91	13,17	45,09	10,88	Pen-and-Paper
Buhrman [36]	HADS Anxiety	35,23806	21,42855	34,28568	19,0476	33,3333	15,71427	28,5714	15,71427	34,71	14,24	30,95	11,11	Pen-and-Paper
Hunt [50]	ASI-GI	72,5	22,75	47,5	23,25	67,5	24,75	62,5	23,75	60,27	16,26	64,9	17,14	Technology

	ASI-Non GI	50	20,75	35	17,25	48	22,5	49	23,5	41,13	13,26	48,48	16,25	Technology
Ljótsson [52]	VSI	59,59999	20,79999	40,26666	23,73333	57,73332	23,33333	55,86665	24,93333	51,2	15,64	56,86	17,04	Technology
Ruehlman [51]	DASS Anxiety	12,11878	11,40451	10,71405	10,99976	11,26166	10,73786	11,47594	11,28547	11,39	7,92	11,36	7,78	Pen-and-Paper
Turner [91]	Negative mood	32	16	29	21	36	15	35	18	30,9	12,73	35,59	11,52	Technology
Williams [53]	STPI	42,75	15	45,25	17,75	42,25	15,75	46	14,75	43,79	11,46	44,25	10,77	Technology
Fusion	value	**36,91987**	**5,974268**	**30,19186**	**6,204113**	**34,36811**	**5,65548**	**34,79181**	**5,912879**	**33,68**	**4,30**	**34,57**	**4,09**	**Equivalent**
	alpha	35,69188		38,49102		31,98445		34,96213						

Dimension		Catastrophizing												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Buhrman [36]	CSQ - Catastrophizing	45,33329	25,66664	28,66664	17,33332	45,66662	22,99998	40,99996	23,99998	33,89	14,36	43,43	16,61	Technology
Hunt [50]	CPSQ-GI	52,5	12,75	31,25	9,75	52,5	14,25	52,5	14	39,09	7,74	52,5	9,99	Technology
	CPSQ-Non GI	37,5	7,75	30	4	35	8,75	40	10	31,58	3,55	37,17	6,59	Technology
Marceau [82]	PCS	47,5	20	42,5	22,5	47,5	25	45	25	45,29	14,95	46,25	17,68	Technology
Ruehlman [51]	PCP-EA	47,6	27,4	40,9	27,25	43,65	26,3	43,85	25,95	44,23	19,32	43,75	18,47	Pen-and-Paper
Turner [91]	Adapted from PCS + CSQ scale	25	24	18	22	27	22	28	24	21,2	16,22	27,46	16,22	Technology
Fusion	value	**41,54574**	**5,78442**	**30,28492**	**3,497788**	**39,89518**	**6,32607**	**42,6961**	**6,794823**	**33,30**	**2,99**	**41,20**	**4,63**	**Technology**
	alpha	33,45952		12,23452		40,01916		46,16963						

Dimension		Depression												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Berman [49]	CES-D	33,5333	20,83331	28,5333	21,76664	32,3333	17,26665	33,56663	21,19998	31,14	15,05	32,83	13,39	Technology
Buhrman [36]	HADS - depression	32,85711	22,85712	28,5714	22,38093	31,42854	19,52379	25,71426	19,0476	30,67	15,99	28,5	13,63	Pen-and-Paper
Devineni	CES-D	26,33323	18,66659	20,66658	17,83326	23,16657	15,83327	23,83324	20,16659	23,37	12,89	23,42	12,45	Technology

[48]														
Litt [47]	CES-D	24,48324	20,93325	18,38326	17,99993	20,28325	20,08325	18,23326	17,7666	20,98	13,65	19,13	13,31	Pen-and-Paper
Ljótsson [52]	MADRS-S	22,03702	14,99999	12,77777	14,99999	23,14813	14,07406	19,44443	15,92591	17,41	10,61	21,52	10,55	Technology
Lorig [39]	Health distress	48,2	24	40,6	23,6	47,4	23,8	46,8	23,2	44,34	16,83	47,09	16,61	Technology
Marceau [82]	CES-D	4,16665	1	3,83332	1	4,16665	0,83333	3,99998	1,16666	4	0,71	4,11	0,68	Technology
Ruehlman [51]	CES-D	42,63	22,17	37,28	20,85	36,3	21,88	35,82	21,02	39,79	15,19	36,05	15,16	Pen-and-Paper
	DASS - depression	19,78528	15,04729	15,19014	13,14257	17,30914	13,99969	15,80918	13,35685	17,18	9,9	16,52	9,66	Pen-and-Paper
Strom [40]	BDI	15,71427	13,03173	10,99999	11,76189	14,15872	9,06348	12,47618	7,69841	13,12	8,73	13,18	5,87	Technology
Williams [53]	CES-D	25,16657	16,83327	27,33322	19,83325	28,49989	19,16659	29,16655	19,16659	26,07	12,83	28,83	13,55	Technology
Fusion	value	**4,823774**	**0,984651**	**4,374056**	**0,983213**	**4,690459**	**0,821618**	**4,911445**	**1,133313**	**4,60**	**0,70**	**4,77**	**0,67**	**Equivalent**
	alpha	0,969538		0,966708		0,675056		1,284398						

Dimension		Disability												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Buhrman [36]	PAIRS	73,33315	14,5333	70,93316	13,59997	75,06648	14,39996	70,66649	15,46663	72,05	9,93	73,02	10,54	Technology
Devineni [48]	HDI	52,9	18,8	38	19,5	54,2	20,5	49,6	23,1	45,72	13,53	52,17	15,33	Technology
Ljótsson [52]	SDS	42,33329	24,66664	24,99998	24,66664	39,33329	27,33331	37,99996	29,99997	33,67	17,44	38,73	20,2	Technology
Lorig [39]	HAQ	72,33333	34,33333	65,66666	44	71,99999	35	72,99999	35,66666	69,81	27,07	72,49	24,98	Technology
Marceau [82]	ODI	44	4	44	2	50	4	48	4	44	1,79	49	2,83	Technology
Ruehlman [51]	Perceived disability	59,6	29,6	51,55	30,6	53,2	29,3	51,75	29	55,71	21,28	52,47	20,61	Pen-and-Paper
Strom [40]	HDI	47,47	12,75	40,55	15,57	45,42	21,32	36,4	22,07	44,69	9,86	41,07	15,33	Pen-and-Paper
Turner [91]	Adapted from SOPA Disability scale	28	25	24	24	31	25	33	26	25,92	17,31	31,96	18,02	Technology
Fusion	value	**46,4421**	**3,503954**	**44,25797**	**1,934828**	**51,27323**	**3,607928**	**48,86131**	**3,647281**	**44,77**	**1,69**	**50,08**	**2,56**	**Technology**

	alpha	12,2777		3,743558		13,01714		13,30266						
Dimension		Interference - I												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Hicks [54]	PedsQL-child	75,6	14,7	76,3	15,3	79,1	11,7	77,7	14	75,94	10,6	78,52	8,98	Pen-and-Paper
	PedsQL-parent	72,9	13,5	77,9	13,2	76,1	13,5	80,2	9,8	75,46	9,44	78,79	7,93	Pen-and-Paper
Lorig [39]	Activity limitation	79,25	24,33	77,5	24,28	80,5	22,58	85,5	46,25	78,37	17,19	81,46	20,29	Pen-and-Paper
Schurman [35]	PedsQL Emotional - child	63	16,53	64,44	29,94	66,5	19,01	70	30,1	63,34	14,47	67,5	16,07	Pen-and-Paper
	PedsQL Physical - child	68,75	15,87	68,4	30,76	74,06	8,72	77,78	15,34	68,68	14,1	74,97	7,58	Pen-and-Paper
	PedsQL Social - child	80,5	14,99	78,33	16,58	84,5	14,03	85,56	19,6	79,52	11,12	84,86	11,41	Pen-and-Paper
	PedsQL School - child	57	22,88	70,56	11,84	61	21,71	73,33	16,96	67,7	10,52	68,66	13,37	Pen-and-Paper
	PedsQL Emotional - parent	55,5	18,77	79,44	14,67	46	21,96	56,67	19,53	70,36	11,56	51,96	14,59	Technology
	PedsQL Physical - parent	75	17,24	90,28	12,54	60,94	19,45	65,63	19,52	84,99	10,14	63,28	13,78	Technology
	PedsQL Social - parent	86,5	10,55	87,78	17,34	77	20,3	77,22	23,47	86,85	9,01	77,09	15,35	Technology
	PedsQL School - parent	64	17,45	73,89	24,21	59	20,92	72,22	16,6	67,38	14,16	67,11	13	Technology
Fusion	value	**73,45577**	**4,752946**	**78,60134**	**4,957498**	**72,89529**	**4,597887**	**75,57996**	**5,122788**	**75,92**	**3,43**	**74,09**	**3,42**	**Equivalent**
	alpha	22,5905		24,57678		21,14056		26,24296						
Dimension		Interference - II												
Study	Variable	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated Value	SD	Aggregated Value	SD	
		Value	SD	Value	SD	Value	SD	Value	SD					
Berman	BPI	42,1	27,4	30	24,1	39,5	21,6	30,7	22,4	35,28	18,1	35,26	15,55	Pen-and-

[49]	Interference													Paper
Buhrman [36]	MPI Interference	59,99998	19,99999	53,33331	23,33332	64,99997	21,66666	58,33331	19,99999	57,18	15,19	61,4	14,7	Technology
Litt [47]	MPI interference	30,49999	22,49999	27,49999	22,49999	17,83333	12,99999	16,66666	15,99999	29	15,91	17,37	10,09	Pen-and-Paper
Marceau [82]	BPI Interference	62	22	59	21	65	21	63	21	60,43	15,19	64	14,85	Technology
Palermo [37]	CALI	18,40625	15,375	11,25	8,9375	19,6875	14,40625	20,6875	14,875	13,06	7,73	20,17	10,35	Technology
	CALI-retrospective	64,1875	18,125	39,65625	19,65625	58,8125	20,59375	50	19,8125	52,91	13,32	54,24	14,28	Technology
Ruehlman [51]	PCP-S Interference	69,52758	19,38883	61,97205	23,9166	64,41649	21,77772	60,69427	23,52771	66,53	15,06	62,7	15,98	Pen-and-Paper
Turner [91]	Interference	26	22	24	25	28	21	30	24	25,13	16,52	28,87	15,8	Technology
Williams [53]	SF-36: physical	38,9	8,6	41,1	8,7	38,9	9,5	38,9	8,6	39,99	6,12	38,9	6,38	Pen-and-Paper
Fusion	value	**42,89006**	**5,472189**	**32,2014**	**5,033551**	**38,18406**	**5,338293**	**38,03578**	**5,360774**	**37,10**	**3,70**	**38,11**	**3,78**	**Equivalent**
	alpha	29,94485		25,33664		28,49738		28,7379						

4 DISCUSSIONS

Some potentials and risks related to mobile and web-based systems were obtained from the full text evaluation of included studies. Firstly, the usage of ED may produce more reliable data compared to PD. Secondly, ED and IdT may result in real-time analyses and subsequent agile treatment adjustments. Thirdly, ED and IdT may provide time-saving and a cost-efficaciousness medical practices. Nevertheless, training for clinical staff is critical [175], and strongly recommended to promote standardised procedures and adherence [176]. In addition, device failures considered in system design [177], should be addressed to avoid missing values and/or prolonged data editing. It should be noted that the use of mobile devices to store health records implies the risk for losing data and personal information, due to its prone to loss. These topics, further the inefficient use of collected data in order to improve treatment effectiveness, were limitations that were detected.

This review included 19 studies related to CBT, in which were noted the effectiveness for decreasing chronic pain, in line with [41,178,179], reducing pain related behaviours as suggested by [180,181], and facilitate return to work, as presented by [182,183]. In spite of, its absence in these studies, innovative CBT such as serious games [184,185] and augmented reality [186,187], seems to be promising. Serious games are the application of motivational aspects of gaming to encourage positive health behaviours [188], whereas augmented reality provides virtual environments combined with touch sensations resulting from interacting with real objects [189]. Further work is needed to understand how these technologies can aid the transformation of CBT delivery models.

The use of SMS [190] to collect data, as proposed by [60,61,70,74], and to deliver CBT, as suggested by [55], may improve treatment outcomes, due to the fact that tailoring messages to individuals may lead to effective health behaviour changes [191–193].

Only one study [81], refers data integration with other systems such as PHR, which suggests limitations on access to the collected data. In addition, some mobile-based systems were designed to interact directly to patients without presence of a healthcare professional [194,195] and/or without evidence of reliability and accuracy. However, as the pain is a multifaceted experience, its therapeutic tends to involve many healthcare professionals and different expertises whereby the data integration may result to the reduction of self-diagnosing that are not regulated [196]. Therefore, it is desirable that patient information may be obtained and delivered both easily and safely (e.g. avoidance of medical examination redundancy, faster patient profile acquisition, and permanent

storage of clinical records) which raises some concerns and challenges related to security aspects such as privacy and confidentiality [197], and communication methods between healthcare professionals and patients.

In line with this, being cloud computing an emerging technology that provides elastic infrastructure, efficiency of resource utilization [198], it appears to be a promising solution for design, development and integration of systems. This technology may enable scalable, portable, and interoperable mobile and web-based systems so as to deliver clinical solutions to the patients, anytime and anywhere [199]. In addition, social media websites are the latest technological development that has been useful in the last years to improve networking and communication [200] (e.g. facebook, twitter) and represent a new source of information and knowledge. Therefore, is expected that clinical systems advance to interact with patients via social media, so as to provide CBT, serious games, self-help, symptoms information and multimedia content. Thus, new studies should be addressed to determine the real benefits and disadvantages of treatments delivery using social media.

Finally, our meta-analysis demonstrated that the effects of technology and pen-and-paper should be obtained not only based on the comparison of the standard deviations together with the values of the mathematical expectations but also considering the condition (P) as described in section 2.7. In fact, was found that technology is favourable for two dimensions of pain, such as catastrophizing and disability, in addition to produce an equivalent outcome compared with pen-and-paper for anxiety, depression, interference and pain intensity. When technology and pen-and-paper present equivalent outcomes that may suggest not only that technological systems are feasible, but also that are room for improvement so as to produce significant effects in patients' conditions and welfare. Moreover, further studies should be addressed to determine the side effects of the application of technology in economic, medical, educational, and social topics.

5 CONCLUSIONS

This review distinguished mobile and web-based systems related to chronic pain complaints. Sixty-two studies were examined and the main findings are summarised as follows:

- (RQ1) Sixty-two studies were included encompassing 13,338 participants. A total of 50 (81%) related to mobile systems, and 12 (19%) related to web-based systems.
- (RQ2) The data extracted from the included studies, revealed the use of almost ninety different scales and questionnaires at pre/post/during treatment. The data collected

comprised among others: location, duration, and intensity of pain, consequences as the impact on quality of life, emotional and aversive aspects. This highlights the multi-dimensional condition of pain.

- (RQ3) Forty-four percent of mobile systems (19 of 43) transmitted data immediately after its acquisition, via Internet, upload through personal computer or SMS. The remaining twenty-four studies, three did not report the transmission method, whereas twenty-one, collected data at intervals, in the clinic visit or at the end of the study.
- (RQ4) The meta-analysis obtained from the selected RCTs (16 studies) evidenced favourable effect of technology in two dimensions of pain: catastrophizing and disability. Pen-and-paper and technology revealed equivalent effect in the remaining dimensions, such as: anxiety, depression, interference and pain intensity.
- (RQ5) The proposed qualitative analysis model stemming from the data fusion method showed to be suitable when combined with a quantitative model based on the comparison of the standard deviations together with the values of the mathematical expectations.

Despite these findings, effects of technology on practitioners and patients outcomes remain understudied, and their promising to increase self-care and accurate monitoring mostly untested. In addition, data integration raises several concerns and challenges to the design, development and application of monitoring systems applied to pain.

5.1 Limitations

Some limitations of this review should be mentioned. First, only English-language publications were included. Second, the lack of technical explanations related to data acquisition, transmission and storage, restricted its analysis and extraction. Third, the quality assessment should be interpreted with caution due to the fact that the defined criteria may have introduced some subjectivity. Fourth, several RCTs included in meta-analysis had risk of bias, however we assumed that they are statistically independent. Fifth, the null hypothesis was considered, that means, all sample data are assumed to be sufficient.

5.2 Conflict of interest statement

No conflicts of interest.

5.3 Author's contributions

Conception and design: Joaquim Viana, Nuno Pombo;
Search databases: Nuno Pombo;
Drafting of the article: Nuno Pombo;
Statistical data fusion: Kouamana Bousson;
Analysis and interpretation of the data: Kouamana Bousson, Nuno Pombo, Pedro Araújo;
Critical revision of the article: Joaquim Viana, Kouamana Bousson, Pedro Araújo;
Final clearance of the article: Joaquim Viana, Pedro Araújo.

5.4 Summary Table

What was already known on the topic:

- Self-report is considered the most accurate pain assessment method, so that the patients should be asked to periodically rate their pain severity and related symptoms;
- Handheld devices and IdT were largely used to chronic pain monitoring encompassing several purposes, such as: education, reminders, feedback, and disease control;
- The adoption of technology allowed the development of electronic pain diaries (ED) as computerised version of paper pain diaries (PD) and enables patients either to report complaints close in time that pain occurs, called ecological momentary assessment, or to address retrospective pain, that consists in pain recall over some period of time;
- Pain results from multiple aspects, such as sensory (e.g. location, intensity), affective (e.g. depression, anxiety) and cognitive (e.g. quality of life).

What this study added to our knowledge:

- Favourable effect of technology in two dimensions of pain: catastrophizing and disability. Pen-and-paper and technology revealed equivalent effect in the remaining dimensions, such as: anxiety, depression, interference and pain intensity;
- The description of the collected data at pre/post/during treatment, comprising almost ninety different scales and questionnaires which include the following topics: location, duration, and intensity of pain, consequences as the impact on quality of life, emotional and aversive aspects;
- Lack of data integration, accessibility and share to and from healthcare profissional and patients;

- The proposed qualitative analysis model stemming from the data fusion method showed to be suitable when combined with a quantitative model based on the comparison of the standard deviations together with the values of the mathematical expectations.

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APPENDIX I Electronic search

The search was conducted in the scientific electronic databases using SCIRUS web site (scirus.com).

Mobile systems search:

(("cellphone") OR ("cell phone") OR ("mobile phone") OR ("mobile device") OR ("smartphone") OR ("pocket PC") OR ("pocket computer") OR ("personal digital assistants") OR ("personal digital assistant") OR ("pda") OR ("handheld computer") OR ("hand held computer") OR ("tablet pc")) AND ("chronic pain")

Web-based systems search:

(("Internet intervention") OR ("Internet treatment") OR ("Internet monitoring") OR ("Internet self-reporting") OR ("web-based intervention") OR ("web-based treatment") OR ("web-based monitoring") OR ("web-based self-reporting") OR ("web based intervention") OR ("web based treatment") OR ("web based monitoring") OR ("web based self-reporting") OR ("online intervention") OR ("online treatment") OR ("online monitoring") OR ("online self-reporting") OR ("web treatment") OR ("web intervention") OR ("web monitoring") OR ("web self-reporting")) AND ("chronic pain")

APPENDIX II Quality assessment tool

1. Formulation of the research question
2. Specification of inclusion/exclusion criteria
3. Sample description
4. Design
5. Technical description
6. Description of study procedure
7. Statistical analyses
8. Conclusions supported by data
9. Limitations of study analysed explicitly
10. Research questions are answered

APPENDIX III Risk of bias assessment

Study/Year	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Free of selective outcome reporting	Free of other sources of bias
Berman [49], 2009	Yes	No	No	Yes	Yes	No
Buhrman [36], 2004	Yes	Yes	No	Yes	Yes	Yes
Devineni [48], 2005	No	Yes	No	Yes	Yes	Yes
Hicks [54], 2006	Yes	Yes	No	No	Yes	Yes
Hunt [50], 2009	Yes	Yes	No	No	Yes	No
Litt [47], 2009	Yes	Yes	No	Unclear	Yes	Yes
Ljótsson [52], 2010	Yes	Yes	No	Unclear	Yes	Yes
Lorig [39], 2008	Yes	Yes	No	No	Yes	Yes
Marceau [82], 2010	Yes	Yes	No	No	Yes	Yes
Oerlemans [38], 2011	Yes	Yes	No	Unclear	Yes	No
Palermo [37], 2009	Yes	Yes	No	Yes	Yes	Yes
Ruehlman [51], 2012	Yes	Yes	No	Yes	Yes	No
Schurman [35], 2010	Yes	Yes	No	Yes	Yes	Yes
Strom [40], 2000	Yes	Yes	No	Yes	Yes	No
Turner [91], 2005	No	Yes	No	Yes	Yes	Yes
Williams [53], 2010	Yes	Yes	No	Unclear	Yes	Yes

Chapter 4

Interdisciplinary Concept Transfer from Aerospace Sciences to Medical Decision-making Based on Multisensor Data Fusion

This chapter consists of the following article:

Interdisciplinary Concept Transfer from Aerospace Sciences to Medical Decision-making Based on Multisensor Data Fusion
Nuno Pombo, Kouamana Bousson, Pedro Araújo, and Joaquim Viana
Informatics for Health and Social Care, accepted for publication, 2013.

According to 2012 Journal Citation Reports published by Thomson Reuters in 2013, this journal scored ISI journal performance metrics as follows:

ISI Impact Factor (2012): 1.273

ISI Article Influence Score (2012): 0.416

Interdisciplinary Concept Transfer from Aerospace Sciences to Medical Decision-making Based on Multisensor Data Fusion

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ABSTRACT

In the last years, Internet-delivery treatments were largely used to pain monitoring, offering to health care professionals and patients the ability of interact anywhere and at anytime. Electronic diaries have been increasingly adopted as preferred methodology to collect data related to pain intensity and symptoms and thus, replacing the traditional pen-and-paper diaries. Based on the capabilities provided by the aerospace systems this paper presents a methodology supported on multisensor data fusion to evaluate the effects of electronic and pen-and-paper diaries on pain. We examined studies published in English, of randomised controlled trials representing computerised systems related to chronic pain complaints that included data collected via Internet. These studies were obtained in the following data sources: BioMed Central, PubMed Central and ScienceDirect, from 2000 up until 30th June 2012. Based on comparisons of the reported pain intensity collected during pre and post-treatment in both control and intervention group, the proposed multisensor data fusion model revealed that the benefits of technology and pen-and-paper are qualitatively equivalent $(50,68 \in [53,2 \pm 3,59] \; and \; 53,2 \in [50,68 \pm 3,72])$. We conclude that the proposed model revealed to be suitable, intelligible, easy to implement and low time and resources consuming.

Keywords: Aerospace systems, multisensor, data fusion, medical decision-making, pain assessment, electronic pain diary

1. Introduction

Emerging solutions based on Internet are becoming increasingly used to pain monitoring, leading to a new care model based more on contacts than on visits [1] and offering to health care professionals (HCP) and patients the ability to interact with the system anywhere and at anytime. This ubiquity presents invaluable opportunities, such as self-reporting of complaints, that is considered the most accurate pain assessment method [2], education, reminders, feedback, disease control either to inpatients or at patients' home. Thus, patients are enable to periodically rate their pain severity and related symptoms using combined electronic versions of scales (e.g. Numeric Rating Scale [3], Visual Analogue Scale [4]) and questionnaires (e.g. McGill Pain Questionnaire [5], Brief Pain Inventory [6]) representing electronic pain diaries (ED) instead the usual pen-and-paper diaries (PD). However, the assessment of ED in comparison with PD are not clear nor easy to determine as well as the effects of computerised monitoring systems on practitioners and patients outcomes, remain understudied and their promising to increase self-care and accurate monitoring mostly untested. Therefore, are promising methodologies that enable these assessments in a reliable way. The main challenges lie not only in the difficulty in quantifying the pain due to its subjectivity [7], but also in designing models with capability to compute and interpret the data collected from different and heterogeneous sources. It is crucial that the assessment model should focus on individual patient data as well as on the aggregate collected data obtained from all patients.

Aerospace systems are known to deal with different complex data sources with varied complexities and accuracies (see Figure 1). Because of the criticality of aerospace systems and the precision that is required from these systems, multisensory data fusion methods have been developed to come up with the accuracy and reliability problems encountered in guidance, navigation and control applications.

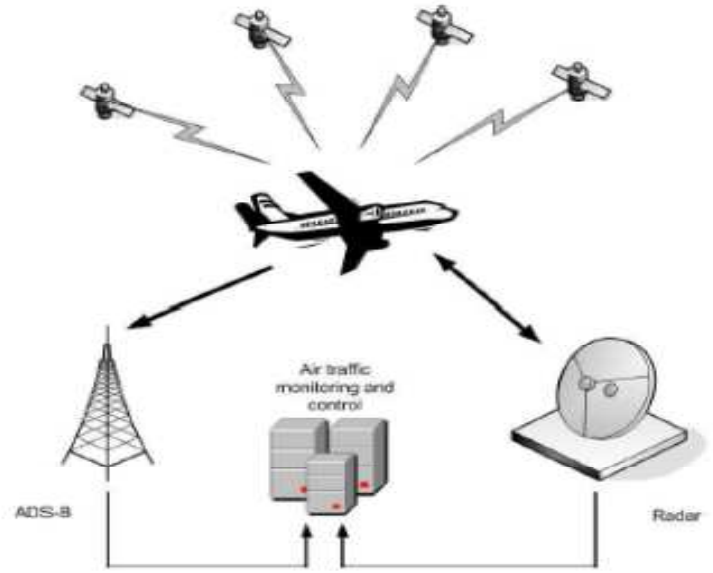

Figure 1: Aerospace data fusion from heterogeneous sources. The aircraft combines the data provided by different sources such as radars and satellites so as to produce information required to the Automatic dependent surveillance-broadcast (ADS-B).

Thus, data fusion is a technique that combines multiple data sources so as to make better inferences than could be achieved from a single source of data [8], in other words, to improve the available knowledge, to update the current information or improve generic knowledge by means of data [9]. Data fusion methods are used in several high-technology fields including decision making, data mining, robotics, video and image processing, to name a few. A statistical advantage is gained due to the fact that data fusion enabled the addition of N independent observations (assuming the data are combined in an optimal manner) that are equivalent to combine N observations from an individual source. The different sources may observe the same scene or at least partially, or they may have different resolutions, accuracies and points of view [10]. The fusion methods vary between centralised and distributed approaches which main purpose is to obtain the globally optimal state. The centralised data fusion combines local measurement data so as to obtain the optimal state whereas, this state is obtained considering different estimators in distributed data fusion methods. Although this method offer a reduced computational burden compared with the centralised method, it requires estimators which may lead to more complex and difficult computation. Distributed methods may promote an easier fault detection and isolation, and it may increase the

input data rates considerably. Moreover, it may provide a higher scalability and robustness to centralised methods. The literature review, as shown in Table 1, revealed several methods applied to data fusion which were clustered, according it nature and characteristics, in the following topics: probabilistic, statistic, knowledge-base theory and evidence reasoning. This review aims at presenting the main advantages and limitations of the different approaches. As example, Bayes analysis in spite of the possibilities for model estimation, it requires a priori probabilistic characteristic of the system which is unknown in general.

In summary, the data fusion models should contains the following characteristics: be able to reduce the effects of impreciseness and uncertainty in the measurements, ability to distinguish ambiguities and inconsistence, adaptability to timing variations in data, and capability to deal with the calibration error induced by each source. Thus, our approach is based on quantitative and qualitative model so as to produce an accurate and a reliable assessment of technology in comparison with pen-and-paper.

The organization of the paper is as follows. Section 2 presents the data fusion concepts and Section 3 describes the proposed analysis proceeding based on statistical models. Section 4 provides the methodology of search and inclusion of studies. The results are presented in Section 5. Finally, discussions and conclusions are given in Section 6.

Table 1: Data fusion methods: advantages and limitations

Group/Methods	Advantages	Limitations	Systems
Probabilistic			
Bayes Analysis	> Provides principled methods for the model estimation	> Requires a priori probabilistic knowledge of information which is not always available or realistic	[11,12]
k-Nearest-Neighbor (kNN)	> Allows unsupervised classification	> Classification depends on the starting point.	[13]
Kalman/Linear Quadratic Estimation /Extended Kalman Filter (EKF)	> Estimates state of variables >Increases the number of data without changing it structure and the algorithm > Reduce errors in the fused location estimate > Produces a fused covariance matrix that better reflects the expected location error	> Unsuitable for large scale systems > Requires a priori knowledge of the uncertainties co-variance matrices related to the system model and its measurements	[14,15]

Statistic			
Cross-covariance	> Accuracy, due to the fact that reduces the prediction error	> Complex and difficult computation required to obtain the cross-variance	[16]
Covariance Intersection	> High accuracy compared with other local estimator > Robustness with respect to unknown cross-covariance	> Complexity and larger computational burden	[17]
Knowledge Base Theory			
Fuzzy Logic	> Allows the inclusion of uncertainty and imprecision > Easy to implement	> The knowledge extraction requires the intervention of human expertises (e.g. physicians) which may take time and/or may give rise to interpretation bias	[18]
Neural Networks	> Learning ability > Robustness to noisy data and its ability to represent complex functions	> Difficulty in determining the adequate size of the hidden layer > Inability to explain decisions > Lack of transparency of data	[19,20]
Evidence Reasoning			
Dempster-Shafer	> Assigns a degree of uncertainty to each source	> Requires assigning a degree of evidence to all concepts	[21]

2. Data Fusion in Aerospace Systems

The proposed mathematical model is based on the data fusion methods described in [22–24] and summarized below. This approach aims at fusing multisensor data obtained from various sources so as to increase the accuracy of system parameter and state estimation. The data are collected and computed in order to determine the mean and the standard deviation representing then the aggregate estimation.

Let us consider n sets of data samples each of which has a Gaussian distribution $N(\bar{x}_i, \sigma_i)$, where $\bar{x}_i$ and σ_i are respectively the mean (or mathematical expectation) and the standard deviation of samples in set i. Then, the probability distribution of the aggregated set is Gaussian with mean $\bar{x}_i$ and standard deviation σ computed as

$$\bar{x} = \sum_{i=1}^{n} a_i x_i = \alpha \sum_{i=1}^{n} \frac{x_i}{\sigma_i^2}$$

where a_i is defined by

$$a_i = \frac{1}{\sigma_i^2}\alpha,\ i = 1,\ldots,n$$

$$\alpha = \left(\frac{1}{\sigma_1^2} + \frac{1}{\sigma_2^2} + \ldots + \frac{1}{\sigma_N^2}\right)^{-1}$$

$$\sigma^2 = \sum_{i=1}^{N} a_i^2 \sigma_i^2$$

3. Qualitative Analysis

The mean and the standard deviation, computed as described in the last section, are used for the qualitative analysis method, that we proposed below, which aiming to produce a more accurate outcome.

Let us consider:

σ_T: standard deviation of technology outcome;

σ_P: standard deviation of pen-and-paper outcome;

$\bar{x}_T$: mathematical expectation of technology outcome;

$\bar{x}_P$: mathematical expectation of pen-and-paper outcome;

Consider furthermore the following conditions:

Condition (P): $\bar{x}_P \in \left[\bar{x}_T - \sigma_T, \bar{x}_T + \sigma_T\right]$ or $\bar{x}_T \in \left[\bar{x}_P - \sigma_P, \bar{x}_P + \sigma_P\right]$ for instance as shown in Figure 2 where $\bar{x}_T = 3, \bar{x}_P = 2, \sigma_T = 1.2, \sigma_P = 0.6$

The opposite condition is pictured in Figure 3 with $\bar{x}_T = 3, \bar{x}_P = 1, \sigma_T = 0.9, \sigma_P = 0.8$.

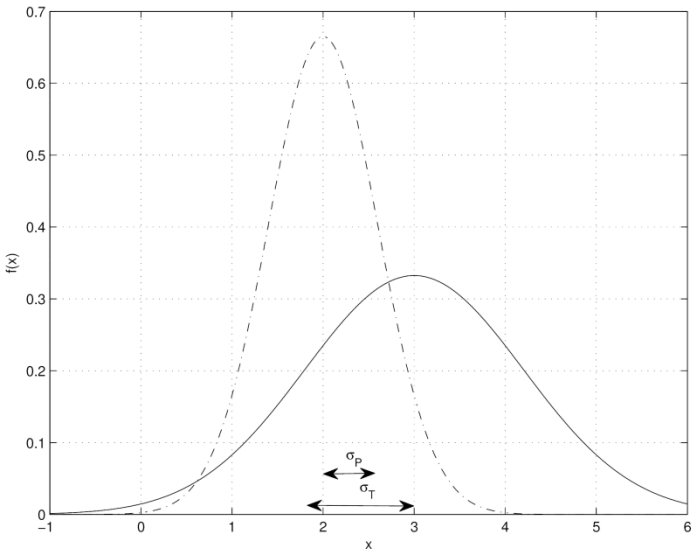

Figure 2: Technology and pen-and-paper are qualitatively equivalent

$$(\bar{x}_T = 3, \bar{x}_P = 2, \sigma_T = 1.2, \sigma_P = 0.6, \bar{x}_P \in \left[\bar{x}_T - \sigma_T, \bar{x}_T + \sigma_T \right])$$

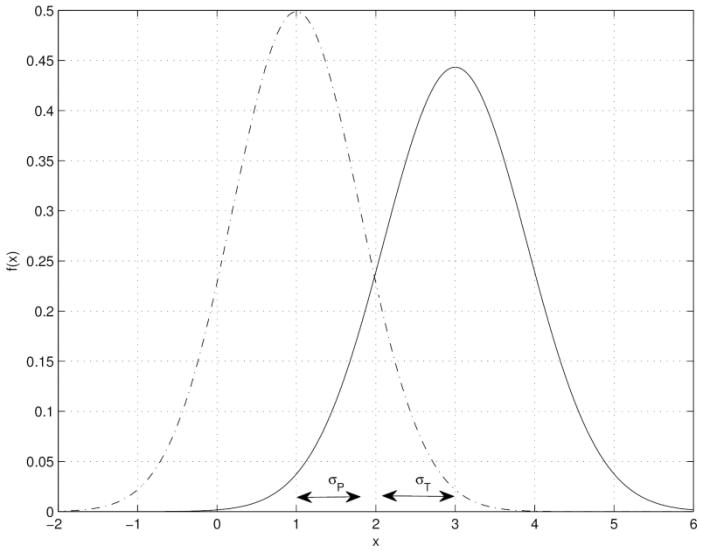

Figure 3: Technology and pen-and-paper are qualitatively different

$$(\bar{x}_T = 3, \bar{x}_P = 1, \sigma_T = 0.9, \sigma_P = 0.8, \bar{x}_P \notin \left[\bar{x}_T - \sigma_T, \bar{x}_T + \sigma_T \right], \bar{x}_T \notin \left[\bar{x}_P - \sigma_P, \bar{x}_P + \sigma_P \right])$$

The rational of condition (P) is that since the standard deviation σ is the average magnitude of the sample dispersion with respect to its mean value $\bar{x}$ (mathematical expectation), any value x that is located at a distance from $\bar{x}$ less than the standard deviation (that is, $|x - \bar{x}| < \sigma$) may be considered as *qualitatively* equal to $\bar{x}$.

From condition (P) described above, a qualitative analysis is performed to know which one among *technology* and *pen-and-paper* provides the best way to get fair results in pain monitoring.

CASE 1: when the lower mean value (mathematical expectation) implies better results:
If condition (P) is verified, then using technology or pen-and-paper gives rise to the same conclusion, even though the mean values may be different;

else if $(\bar{x}_T < \bar{x}_P)$

then technology provides better results than pen-and-paper;

else pen-and-paper provides better results than technology.

CASE 2: when the higher mean value (mathematical expectation) implies better results:
If condition (P) is verified, then using technology or pen-and-paper gives rise to the same conclusion, even though the mean values may be different;

else if $(\bar{x}_T > \bar{x}_P)$

then technology provides better results than pen-and-paper;

else pen-and-paper provides better results than technology.

4. Methods

4.1. Search Strategy

In order to determine the state-of-the-art related to monitoring systems applied to chronic pain a search was conducted in the following electronic databases: BioMed Central, Pubmed Central, and ScienceDirect. Only the randomised controlled trials (RCTs) studies published from 2000 up until 30th June 2012 meeting the inclusion criteria were considered to this study. Every study was independently evaluated by two reviewers (NP and PA) and its suitability determined with the agreement of both parties. A third reviewer (JV) was considered to adjudicate on differences of opinion but was not required because a consensus was reached.

4.2. Search Criteria

Studies were included in this review if they met the following criteria: (1) presented RCTs, (2) based on computerised systems related to chronic pain complaints, (3) included data about pain assessment and (4) were achieved via web-based forms, (5) preliminary or definitive results were presented, and (6) were written in English. These criteria were also applied to studies obtained from reference tracking. There were no age or disease restrictions: participants could be either adults or children, might comprise chronic pain patients or healthy individuals with pain complaints.

4.3. Analysis

The proposed statistical model aims to determine the effects of technology compared with pen-and-paper across the included RCTs. This analysis is based on the self-reporting pain intensity collected during pre and post-treatment in both intervention group (IG) and control group (CG). The participants of IG use ED to report the pain whereas PD are used by the participants of CG. Since less pain intensity values implies better results then, as described in section 2, the condition (P) should be combined with the CASE 1.

In addition, due to the fact that different scales were used across the studies, the pain intensity were converted to a 0–100 scale.

5. Results

As illustrated in Figure 4, our review identified 99 unique citations, of which 67 were excluded as a result of screening, in terms of title, abstract, and keywords. Full text evaluation of the remaining 32 papers resulted in the exclusion of 25 papers that did not match the defined criteria. In addition, the reference tracking allowed for the inclusion of 2 additional papers, thus a total of 9 studies were analysed and the extracted data were tabulated as shown in Table 2. The included studies encompass a total of 1673 participants distributed between CG and IG wherein a web site was used to deliver treatments.

The included studies comprise online questionnaires and therapies based on tailored exercises according to participants' symptoms, multimedia content, information and lessons about physical, cognitive, behavioural and motivational topics. Seven studies [25–31] presented systems that combined emails or phone calls jointly with Internet

(78%). Five studies adopted emails [25,27,29–31] and three of them also performed phone calls [29–31], so as to remind patients to use and/or interact with the system. Moreover, two studies used emails to obtain data [29,30], and to support the system handling [25,26], and together with phone calls, were administered to establish contact between healthcare professionals and patients [26,28].

As shown in Table 3, three studies presented favourable effects to pen-and-paper compared with technology, particularly [28,30] presented lower pain intensity and [32] exhibited smaller retrospective pain. On the contrary, [25–27,29,31–33] presented favourable effects to technology compared to pen-and-paper, in terms of reported pain intensity. For example in [27], the IG (technology) evidenced a reduction on the reported pain intensity from $(31,8 \pm 17)$ to $(18,6 \pm 13)$ at pre and post-treatment respectively. Similarly, the CG (pen-and-paper) presented a reduction on the same criteria from $(35,5 \pm 15,5)$ from $(30,6 \pm 14,7)$ at pre and post-treatment. The aggregate values obtained were $(23,47 \pm 10,33)$ and $(32,92 \pm 10,67)$ related to technology and pen-and-paper respectively, and therefore is considered that this study is favourable to technology due to the fact that presents a qualitatively better outcome than pen-and-paper. On the contrary, the study [30] presented a variation from $(76,46875 \pm 9,71875)$ to $(71,09375 \pm 12,9375)$ in terms of IG at pre and post-treatment. This variation is also presented in CG from $(74,78125 \pm 10,90625)$ to $(71,65625 \pm 13,28125)$. These outcomes resulted in the following aggregate values: $(74,53 \pm 7,77)$ and $(73,52 \pm 8,43)$ related respectively to technology and pen-and-paper. Thus, that this study is favourable to pen-and-paper due to the fact that presents a qualitatively better outcome than technology.

Instead of to determine these effects based on a unique data source, defined by the pre and post-treatment outcomes reported in every study, the proposed multisensor data fusion model is based on multiple data sources representing the different studies so as to produce higher accurate results. In line with this, the quantitative and qualitative analysis reveals that the benefits of technology and pen-and-paper are qualitatively equivalent $(50,68 \in [53,2 \pm 3,59] \; and \; 53,2 \in [50,68 \pm 3,72])$. In addition, the smaller standard deviation of the overall result evidenced that the outcome obtained from the data fusion is more accurate than the local outcomes presented in each study.

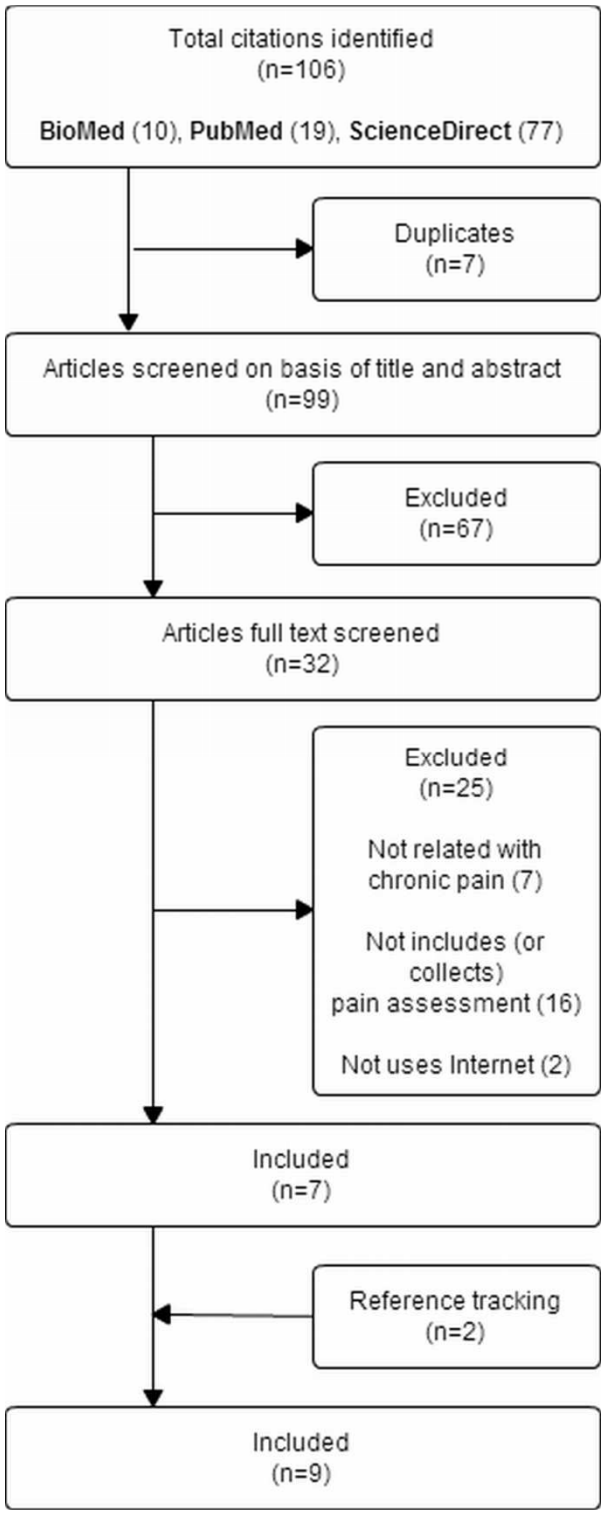

Figure 4: Selected Studies

Table 2: Included RCTs

Study/Year	Condition	Population Participants (Mean age, SD)	
		Intervention Group	Control Group
Berman [25], 2009	Chronic pain	41 (64.3)	37 (67.5)
Buhrman [26], 2004	Low back pain	22 (43.5 ± 10.3)	29 (45.0 ± 10.7)
Devineni [27], 2005	Recurrent headache	39 (43.6 ± 12.0)	47 (41.0 ± 11.8)
Hicks [28], 2006	Pediatric recurrent paint	25 (12.1 ± 2.0)	22 (11.3 ± 2.2)
Ljótsson [29], 2010	Recurrent abdominal pain	42 (36.4 ± 10.1)	43 (32.8 ± 8.6)
Lorig [33], 2008	Fibromyalgia and osteoarthritis and rheumatoid arthritis	422 (52.2 ± 10.9)	433 (52.5 ± 12.2)
Palermo [32], 2009	Idiopathic pain	26 (14.3 ± 2.1)	22 (15.3 ± 1.8)
Ruehlman [30], 2012	Chronic pain	162 [19..78]	143 [19..78]
Williams [31], 2010	Fibromyalgia	59 (50.2 ± 12.3)	59 (50.8 ± 10.6)

Table 3: Comparison between pen-and-paper and web technology using pre and post treatment results by study and overall

Study	Outcome	Technology				Pen and Paper				Technology		Pen and Paper		Favourable to
		Pre treatment		Post treatment		Pre treatment		Post treatment		Aggregated	SD	Aggregated	SD	
		Value	SD	Value	SD	Value	SD	Value	SD	Value		Value		
Berman [25]	PI (mean)	52	19,4	45,6	18,3	54,3	17,4	47,3	18,4	48,61	13,31	51	12,64	Technology
Buhrman [26]	PI (mean)	37,4	18,2	34,3	16,8	44,4	14,2	39,6	16,3	35,73	12,34	42,33	10,71	Technology
	PI	63,33331	31,66665	39,99998	18,33333	83,3333	28,33332	53,33331	13,33333	45,86	15,87	58,77	12,06	Technology
Devineni [27]	PI	31,8	17	18,6	13	35,5	15,5	30,6	14,7	23,47	10,33	32,92	10,67	Technology
Hicks [28]	PI (mean)	48	13	34	24	43	16	47	22	44,82	11,43	44,38	12,94	Pen-and-Paper
Ljótsson [29]	PI	65	42,5	35	37,5	60	37,5	60	40	48,13	28,12	60	27,36	Technology
Lorig [33]	PI	65,3	22,7	58,6	24,4	63,7	22,2	63,4	23,1	62,19	16,62	63,56	16,01	Technology
Palermo [32]	PI	54,5	22,5	35,4	24,2	51,7	16,5	47,6	18,4	45,64	16,48	49,87	12,28	Technology
	RP	66,3	18,7	49,6	21,8	61,6	18,4	54,5	20,4	59,22	14,19	58,42	13,66	Pen-and-Paper
Ruehlman [30]	PI	76,46875	9,71875	71,09375	12,9375	74,78125	10,90625	71,65625	13,28125	74,53	7,77	73,52	8,43	Pen-and-Paper
Williams [31]	PI	51	14	43	16	49	14	49	15	47,53	10,54	49	10,23	Technology
Fusion	value	**57,28429**	**5,05922**	**42,91814**	**5,484841**	**55,41149**	**4,971945**	**50,78559**	**5,198361**	**50,68**	**3,72**	**53,2**	**3,59**	**Equivalent**

PI: **Pain intensity**
RP: **Retrospective pain**
SD: **Standard Deviation**

6. Discussions and Conclusions

In the last years, Internet-delivery treatments were largely used to pain monitoring, offering to HCP and patients the ability of interact anywhere and at anytime. Unsurprisingly therefore, that ED have been increasingly adopted as preferred methodology to collect data related to pain intensity and symptoms and thus, replacing the traditional PD. However, the assessment of ED compared with PD are not clear nor easy to determine. In addition, the effects of computerised monitoring systems on practitioners and patients outcomes, remain understudied and their promising to increase self-care and accurate monitoring mostly untested. In line with this and motivated by the precision and ability to deal with different complexities and accuracies provided by the Aerospace systems, we proposed a centralised quantitative and qualitative data fusion model based on statistical analysis. Instead of acknowledge each study as single qualitative analysis, this model considers it as different data source, leading that the obtained values are higher accurate and represent a reliable assessment. Thus, the examination of the included studies revealed that the benefits of technology and pen-and-paper are qualitatively equivalent. On the one hand this evidenced that ED are feasible to support the monitoring of pain and to replace the usual PD. On the other hand, new studies should be addressed to determine the cost-efficacy resulting from the implementation of these systems.

The proposed multisensor data fusion model showed to be suitable and accurate to determine the effects of technology and pen-and-paper as demonstrated by the lower standard deviation. In addition this method is intelligible, easy to implement (Microsoft Excel was used), and low time and resources consuming.

Some limitations of this study should be mentioned. First, the RCTs included in this study had risk of bias, however we assumed that they are statistically independent. Second, the null hypothesis was considered, that means, all sample data are assumed to be sufficient. Third, despite the multiple dimensions of pain, such as sensory (e.g. intensity), affective (e.g. depression, anxiety) and cognitive (e.g. quality of life), only one outcome, pain intensity, was considered in this study. Thus, further work is needed so as to determine the effects of technology and pen-and-paper across the different dimensions of pain based on the proposed data fusion model.

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Chapter 5

Web Services for Remote Pain Monitoring

This chapter consists of the following book chapter:

Web Services for Chronic Pain Monitoring
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Web Services for Chronic Pain Monitoring

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Abstract. The use of web services allows, anywhere and at anytime, a truly global, platform independent, and interoperable mean to access information. This chapter presents an overview of the key concepts for electronic pain diaries, the role of web services and its integration in the computerized system to monitorize chronic pain patients. The usage of web services may lead to enhance therapeutic assertiveness, through improving the process of acquisition and sending data, as well as the method of receiving alert messages. The effectiveness of this monitoring is particularly important, not only due to the fact that pain is considered the fifth vital sign for representing basic bodily functions, health and quality of life, but also, due to its subjective nature.

Keywords : Chronic pain monitoring; pain diary; mobile health; web services; clinical decision support system;

1.Introduction

Pain is considered the fifth vital sign for representing basic bodily functions, health and quality of life,[1,2] complementing the well-known physiologic parameters of blood pressure, body temperature, pulse rate and respiratory rate. Nevertheless, it is distinguished from these vital signs, insofar it describes a subjective experience and manifests itself in a particular way in

each individual. Actually, the pain relies of physiological, neurological and psychological idiosyncrasies. The International Association for the Study of Pain,[3,4] defines the pain as an unpleasant sensory and emotional experience related to past or potential tissue damage or it may be described through the concepts of tissue damage. When pain occurs quickly and with relatively short duration, is considered as acute pain. On the contrary, when pain manifests itself over a long period of time is regarded as chronic pain,[5] and may be related to a number of different pathological stages and medical conditions such as arthritis, fibromyalgia, migraine, low back pain, among others.

In fact, in accordance with Institute of Medicine (IOM),[6] only chronic pain, affects at least 116 million American adults (circa 37% of total population), surpassing the total affected by heart disease, cancer, and diabetes combined. In addition, the occurrence of chronic pain reduces the quality of life and impairs the working abilities of people,[7] culminating in a high cost, about 635 billion USD per year, in medical treatment and lost productivity. In this sense, computerized monitoring systems for pain management become strategically important, in order to considerable improve benefits for patients and healthcare professionals (HCPs). For the health care system it can contribute to optimization of human and financial resources.

This chapter aims to explain a monitoring system,[8] with particular emphasis on the use of web services (WS), that enable the combination of pain diary with a personal health record (PHR).[9] This way, the following section presents electronic pain diaries, succeeding a section that describes WS concepts, and a section related to the architecture of the proposed system. Finally, are presented future trends and conclusions.

2.Pain Diaries

Since the chronic pain occurs over time, leads to a permanent need for the monitoring of patients by HCPs. In this sense, several daily measurements over a period of time are performed, in order to analyze the pain evolution and its relation to therapy defined by the HCP. These regularly collected data, yield pain diaries and making them a valuable means to assess a patients clinical course and to identify changes in health conditions.

Furthermore, it empowers patients to actively contribute to their health care[10] as well as often providing pragmatic assistance such as medication record and medical appointment reminders.[11] Usually, the input data are based on self-reporting, observation, or even physiological data collected. However, due to the inherent subjectivity of pain it becomes dif-

ficult to determine the right treatments for the patient in which pain is manifested.[12] Thus, it is common practice to use rating scales and questionnaires as a means of measuring pain, such that the pain rating scales have a fundamental place in clinical practice.[13] The pain values can be entered individually or combined with other parameters, physiological or behavioral characteristics of patients, such as physical activity or eating habits.

Figure 1 depicts several types of pain scales, namely: Faces Pain Scale (FPS)[14,15] (the initial version contained 7 faces, but was subsequently adjusted to only 6), Numeric Rating Scale (NRS),[16] and Visual Analog Scale[17] (VAS).

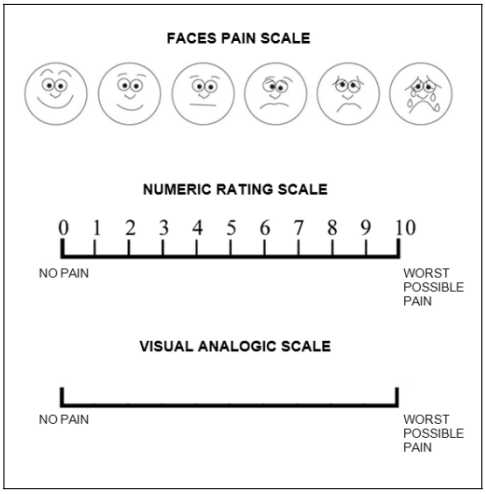

Fig. 1. Illustration of pain scales.

In spite of FPS and VAS having been considered during the development of the computerized system, currently we adopted the NRS in the daily chronic pain software, in order to ask patients to provide reports of their pain. The NRS ranges from 0 to 10, with the lower limit represents "no pain" and the upper limit represents the "worst pain imaginable". It can be stated simplistically that for values reported less than 2 is considered mild pain, for values between 3 and 7 is called moderate pain and for values between 8 and 10 is considered severe pain.

2.1.Related Work

Technology can provide several benefits including clinicians mobility, providing real-time access to data and information, reducing medical errors, saving time, supporting evidence-based practice, enhancing productivity and quality of care, and providing a tool for communication.[18] In this sense, the technological developments lead to pain diaries increasingly based on small, portable computers instead of using pencil-and-paper.[19] This way, the electronic pain diaries can be used to assist patients in assessing and reporting their pain, and beyond that, can help HCPs to deal with pain control in a more structured way.[20]

With this in mind, we developed an innovative system that uses WS in order to provide solutions to several limitations detected in literature, related to computerized pain diaries systems. Firstly, the electronic pain diary presented by Page et al,[21] consists in the software version of the McGill Pain Questionnaire (MPQ),[22] which runs in Microsoft XP Tablet- PC with exporting data capabilities to Microsoft Access. This approach exhibits two drawbacks, including the excessive time to complete the questionnaire (around 20 minutes, derived from the completion of 10 questions related not only with pain, but also with daily habits and symptoms), as well, the absence of real-time analysis by the HCP in relation to recorded data.

For its part, Sufi et al[23] present a system to get the pain value based on mobile devices running software developed in Java 2 Micro Edition (J2ME). The value obtained is sent to a remote server, together with other physiological parameters such as heart rate or oximetry, using Short Message Service (SMS), Multimedia Messaging Service (MMS) or HyperText Transfer Protocol (HTTP). Nevertheless, an important limitation is observed, related to the nonexistent of schedule to patient's data acquisition, which may lead to forgetfulness by the patient, and therefore paucity or even absence of input pain records.

On the contrary, Ghinea et al,[24] present a client-server architecture whose clients are running in Windows CE handheld devices to gather patient's data around the clock. The collected information is sent to the server via an WiFi hotspot using HyperText Transfer Protocol Secure (HTTPS). However, this system presents a significant constraint, since it only sends data at the end of the day to the remote server, therefore, the analysis of data occurs with time lapse in order to the time of editing.

Finally, Bielli et al[25] present a pain diary based on mobile phones, whose pain information is sent to the server using a General Packet Radio Service (GPRS) connection or through web access. A peculiarity of the system is

that it automatically sends SMS or MMS messages, to warn the patient to fill the required data. However, this approach presents a restriction regarding the obligation of data analysis by the HCP before sending messages to the patients, i.e., the system does not allow the generation of automatic responses, making it vulnerable to temporal availability of the HCP.

In summary, the presented system, as described below, takes advantage of WS features to provide real-time analysis and feedback, input data scheduling, and consequent adjustment of the therapy according to health conditions of each patient, along the treatment period. Moreover, this approach may lead to the adoption of WS as a means of integrating the patient's pain diaries in healthcare systems, thereupon, it may contributes to increase the interconnection among systems, and between HCPs and patients. Incidentally, the overwhelming percentage of smartphone downloadable pain management applications encountered in online marketplaces,[11] do not allow sending data to HCPs, neither integration with healthcare systems.

3.Web Services

The usage of WS have transformed the web from a publishing medium used to simply disseminate information, into an ubiquitous infrastructure that supports transaction processing.[26] The main purpose is to ensure interoperability, in other words, the WS provide a standardized mechanism for heterogeneous information systems and applications to communicate with each other. Furthermore, they are used to enable the reuse of application-components, and also to connect existing software, independent of their implementation language, operating platform,[27,28] and location.

The WS involves the presence of a provider, in charge for the service implementation and it availability on the Internet and a client to consume the service. Figure 2 depicts the WS protocol stack, composed by the following elements: discovery, description, messaging, and transport.

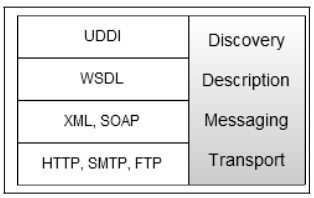

Fig. 2. Protocol stacks of web services.

The discovery layer comprises by the Universal Description Discovery and Integration (UDDI),[29] in order to provide a technical specification for describing and discovering WS providers, as well as their available services. In its turn, the description layer is composed by Web Service Description Language (WSDL),[30] that consists in the definition of the public interface to the WS, in terms of Extensible Markup Language (XML) syntax. The obtained information contains the name, location, the operations exhibited by the WS, and expected inputs and outputs. The messaging layer is responsible for encoding and exchanging data between provider and client. In this sense, is often used the XML, and the Simple Object Access Protocol (SOAP).[26,27] Finally, the transport layer supports several protocols such as HTTP, Simple Mail Transfer Protocol (SMTP), and File Transfer Protocol (FTP), among others.

3.1. XML

XML defines documents in a structured format such as data content and metadata, that enables to exchange information among different computer systems independently of their platform and environment. This structure is composed by labels specified in a tag format, that represent the scheme and the content regarding to the data. Each label is described by a pair of tags, such as <> and </>, that identify respectively the start and the end of the data. The start tag may include a name-value pair termed attribute in order to typify the content of the label. These labels represent a portion of the document and are denominated element. In its turn, the elements are grouped into a hierarchical structure by defining parent-child relationships. The top-level element is called document root and is unique in the XML tree. An example of the XML structure is depicted in Figure 3.

```
<? xml version="1.0" enconding="UTF-8" ?>
<rootelement>
    <element attribute_name="attribute_value">
        <child>This is level 1 of the element</ child>
    </ element>
</ rootelement>
```

Fig. 3. Example of the XML structure.

3.2.SOAP

SOAP is a lightweight protocol that grants an extensible XML framework for message exchange, over a different transport protocols, usually HTTP, in a distributed environment. In fact, it is based on XML and specifies a manner to exchange messages between different processes and/or machines. This specification is called envelope, and it is the root element of the SOAP Message, which purpose is to define the origin, the destination, and the process model through the use of XML to encode data types contained in the messages. The message path is the set of intermediates processes through which the message passes since the origin to the destination.

Fig. 4. SOAP message structure.

The SOAP Envelope, depicted in Figure 4, provides the serialization context and namespace information for data handled in the message, and is comprised by the following elements:

- SOAP Header: Contains the required information about the body content processing, such parameters regarding routing, delivery, authentication and authorization. This is an optional element in SOAP Envelope.

- SOAP Body: Is a mandatory element that includes data, expressed in terms of XML, to be processed and delivered. Optionally, the body can include the fault element, in order to display error messages.

4.System Architecture

The presented approach encompasses a commercial PHR, called Meu Sapo Saúde, provided by PT Comunicações/SAPO Labs, and a mobile application (app) used by the patients as pain diary. Both PHR's module of pain and the app were developed within this research, and are connected through the use of WS. The adoption of WS was due to the fact that they provide the usability and interoperability required to ensure the integration of pain diary records in a remote database associated to PHR. The app was developed for devices with Android OS and includes a SQLite database to store local data. The workflow of the system, depicted in Figure 5, is described as follows.

Firstly, (1) HCPs, using a browser, access to the PHR to define the monitoring plan of each patient in terms of frequency of recorded values and content of automatic messages based on obtained values. (2) This way the app, due to the fact that periodically checks for updates in the PHR, changes the monitoring rules in order to adjust them in agreement with the clinician's indications. (3) The app saves these data internally in a SQLite database. Therefore, over time the individual therapy of each patient tends to remain adjusted according to the evolution of his state of health.

With this in mind, (4) in conformity with the frequency of data recording in the diary of pain defined by the HCP, the system asks the patient to enter the pain intensity. This request is followed by an audible warning and remains on the mobile device's screen over a period of time. After this period, if the patient has not responded, a "no response" is assumed, which will then be statistically analyzed together with other values. Whether a "no response" or a value are entered by the patient, they are (5) immediately recorded in the database of the mobile device, as well as (6) being sent by a WS to the PHR, thereby available for online viewing. If the data transmission is not successful, the records will be marked as pending and the system will try again to send them the next time planned for recording data. (7) Automatically and without requiring intervention by the patient, the system ensures the sending of all data to the PHR and therefore allows a reliable data analysis. (8) Immediately after sending and recording the values of pain, the app will go into background mode until the next moment of data entry. In addition, (9) the app periodically detects, through the WS, the existence of messages in the PHR. These messages may have been caused by (10) the last data recorded or (11) issued by an HCP. (12) Whenever there are messages, they are saved in local database of the mobile device and are presented to the patient. If the app is in background, its activation is following by an audible warning.

Furthermore, (13) the system allows the patient to register unplanned pain records in which submission process is identical to the planned records. These data are classified according to their nature, ie, for analytical purposes each record indicates if it was planned or unplanned. (14) This register of unplanned data can be performed directly in the PHR, by using a browser. At last, (15) all the information generated in the system, such as pain records and alert messages, can be accessed in the PHR, through the use of the browser, either by the patient or by an HCP.

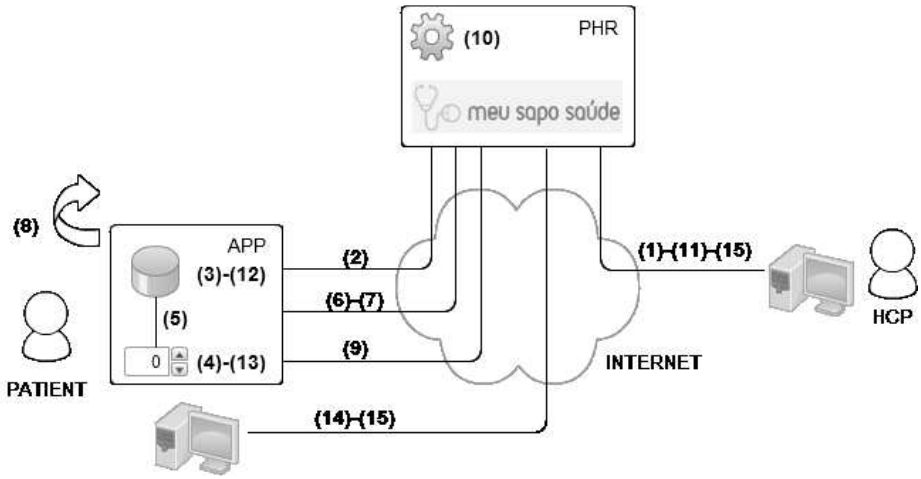

Fig. 5. Workflow of the proposed system.

Taking into account the abovementioned processing, the use of WS, through Internet access allows the user to take advantage of the mobile device's ubiquity and connectivity. In fact, WS enables communication between the app and the PHR, which consists of the execution of several methods, namely:

- Scheduling: Get the data entry frequency around-the-clock. This frequency vary according to the health of the patient;
- Messaging: Obtain messages for the patient. These messages were issued manually by the HCP or automatically by the system;
- Pain Records: Sends the pain records emitted by the patient. The pain records vary between planned and unplanned.

The app sends SOAP messages over HTTP using a standard transport security, such as HTTPS to ensure that a message is protected during transit. In other words, the HTTPS is a point-to-point security, which does not allow intermediaries to act on the data, and requires trust between the HTTPS end-point and the location of the application being secured.[31] In order to inform the app that a message has reached its destination the WS sends a response whose format can either be SOAP or JavaScript Object Notation (JSON).[32] This request-response implementation is called two-way callback-based asynchronous send.[33] The Figure 6 depicts a request and a response in SOAP format, regarding to obtain the pending messages of the patient.

It should be noted that the WS associated with the PHR was developed on Microsoft technology, particularly by using Windows Communication Foundation (WCF).[28,34]

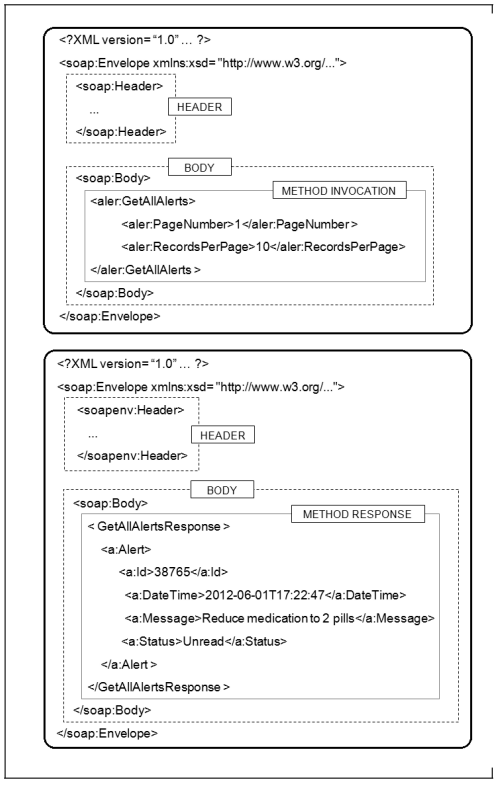

Fig. 6. Example of SOAP request-response message.

In summary, the system presents an easy access to the patient, since it happens not only through the app, but also directly in the PHR. At the same time, is provided a two-way communication between the patient and HCP, to the extent that the data recorded by the first can trigger the issuance of warnings pre-defined by the second. Furthermore, the automation of messages emission will release the HCP's time spent in data analysis and therefore solve one common problem related to the lack of regularity in the visualization and incorporation of obtained data in decision making by the HCPs.[35] Moreover, due to the use of WS, the feedback under normal conditions occurs in real-time. This feature may lead to faster and immediately adjust of the medical procedures after the occurrence of an episode of pain. Additionally, the system allows the patient to register unplanned pain records whenever there is an occurrence of pain. Thus, the monitoring data will be more comprehensive and realistic about the patient's state of health and consequently may result in a higher effectiveness of the therapy defined by the HCP. This way, the user's experience resulting from the interaction with the system will be enhanced, which may lead to increase the adherence of patients.

5.Conclusion

In this paper it was presented the use of WS in order to enhance the features of pain diaries, especially with respect to monitoring and implementation of clinical practice by the HCP. The results obtained in the pilot study are very promising and reveal that this approach, mainly due to the use of WS, allows to solve several problems detected in different papers and reviews. These problems include the lack of timely feedback from the HCP or the adjustment of the system depending on the patient's treatment. Due to the detection and retrieval of messages through the use of WS, it is guaranteed that the patient is alerted in a timely manner with warning messages defined in the system or manually issued by the HCP. Besides, since the system allows the definition of automatic responses according to the values obtained for the pain, it does not require the permanent expenditure of time by HCPs in analyzing and formulating responses. Moreover, the system determines the behavior of the pain diary in terms of frequency of records and display of alert messages, making it an adjustable system to the patient and their therapy.

However, new studies should be addressed to confirm these evidences, so that the system will be deployed in several Hospital Centres to cover a wide range of patients. During this implementation numerous studies should be

performed by a multidisciplinary team of experts, in order to evaluate this system. It should be appraised the usability (of the app and the PHR), economic effects, and the contribution to improve the patient's treatments adherence and the effectiveness of the therapeutics. In this sense, the present system will be complemented with a knowledge based component whose purpose is to analyze and to process the obtained patients' pain records.

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Chapter 6

Evaluation of a Ubiquitous and Interoperable Computerised System for Remote Monitoring of Ambulatory Post-operative Pain: A Randomised Controlled Trial

This chapter consists of the following article:

Evaluation of a Ubiquitous and Interoperable Computerised System for Remote Monitoring of Ambulatory Post-operative Pain: A Randomised Controlled Trial
Nuno Pombo, Pedro Araújo, Joaquim Viana, and Dias Costa
Technology and Health Care (IOS Press), accepted for publication, 2013.

According to 2012 Journal Citation Reports published by Thomson Reuters in 2013, this journal scored ISI journal performance metrics as follows:

ISI Impact Factor (2012): 0.638

Evaluation of a Ubiquitous and Interoperable Computerised System for Remote Monitoring of Ambulatory Post-operative Pain: A Randomised Controlled Trial

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ABSTRACT

Essentially by economical reasons, intending to reduce costs with in-hospital patient accommodations, a permanent pressure was observed in the last years to increase the percentage of surgeries done in ambulatory surgery. The effective control of post-operative pain in this setting is a challenge to all health professionals. Computerised systems are more and more being used for remote patient monitoring including those in post-operative period at home. This study evaluates the feasibility of delivering a computerised system developed by our research team for remote pain monitoring and how much the system is user-friendly and the patient compliance to it. Additionally we comparatively assess if the use of this system increases the quality of pain treatment in ambulatory surgery. Participants included 32 adults, aged 18-75 randomly assigned to a control group or an computerised treatment group. Primary treatment outcome was pain intensity ratings (0-10 NRS) reported several time per day during a five-days monitoring period, using a electronic pain diary combined with a web-based Personal Health Record. Findings demonstrated the feasibility and suitability of the proposed system for pain management. Its handling was revealed user-friendly without requiring advanced skill nor experienced users. In addition, was evidenced that the guidance of health

care professionals is essential to patients' satisfaction and experience stemming from the usage of the system. There were no significant group differences regarding to improvements in the quality of pain treatment, but this can be explained by the small scores of pain registered in both groups, related to the kind of surgical interventions recruited with degrees of pain that usually are easy to be treated. To evaluate benefits on a patient-centered perspective are necessary studies in ambulatory major surgery or in chronic pain, including oncologic and non-oncologic pain resistant to treatments.

Keywords: remote monitoring, electronic pain diary, post-operative, acute pain, clinical decision support system, controlled trial.

1 INTRODUCTION

Surgical procedures almost invariably cause tissue damage that may result in a significant percentage of patients feeling discomfort and moderate to severe pain [1,2], which compelling its management as an essential care component in surgical ambulatory or wards. Pain is highly subjective and difficult to quantify, is an individual and personal experience for everyone [3], that challenges it description, assessment and treatment. In addition, the impact of inadequate pain relief, besides of unethical, may result in earlier discharge from hospital, post-operative complications, negative impact on function and quality of life [4–8], economic burden [9–12], as well as quality of life interference, physically and mentally disorders such as distress or anxiety [13–19]. Moreover, many indicators suggest continued growth in the ambulatory arena [20], essentially due to economical reasons intending to reduce costs with in-hospital patient accommodations.

Thus, electronic diaries were increasingly used in the last years aiming to provide reliable pain assessments, so as to produce high-quality treatments and outcomes. These systems, delivered essentially via mobile devices, were used for numerous purposes such as education, reminders, feedback, and disease control [21]. Firstly, they may promote a faster and easier exchange of information between patient and health care professionals (HCP), that may improves prediction and efficiency of the treatment [22–28]. This may occur when the data are transmitted to HCP so as to provide information when and where it is needed and thus to improve diagnosis quality and knowledge. Secondly, electronic diaries may foment the self-management of pain, due to the fact that they permit collect data at the same moment that pain occurs, also called, ecological momentary assessment (EMA) [29].

However, largely of these systems were designed to interact directly to patients without presence of a healthcare professional [30,31] and/or without evidence of reliability and accuracy. Thus, effects of electronic diaries on practitioners and patients outcomes remain understudied and their promising of increase self-care, acceptability and accuracy of pain monitoring mostly untested.

The aim of our study was to evaluated the feasibility of a computerised system [32], among a clinically referred population of adults with mixed acute post-operative pain conditions. This

system was developed by our research team to allow remote monitoring of pain and encompasses an electronic pain diary, a web-based Personal Health Record (PHR), and a web service (WS) to take advantage of distributed computing, integration of applications and ubiquitous access, anytime and anywhere [33,34]. We also evaluated how much the system is user-friendly and the patients compliance to it. Additionally we comparatively access, in a preliminary controlled randomised trial, if the use of this system increases the quality of pain treatment in ambulatory surgery.

2 METHODS

2.1 Patients

This study was conducted in the Ambulatory Surgery Department of the Hospital Sousa Martins in Guarda, Portugal, and included 37 adults patients submitted to surgical procedures from which a certain degree of pain is expected or possible during the initial post-operative days. Participants were recruited over a six-weeks period through specialty care physician referral from the ambulatory surgery department. The protocol of the study was approved by the appropriate Ethics Committee, and the participants were enrolled after written informed consent.

2.2 Inclusion/exclusion criteria

Inclusion criteria consisted of the following: (1) age ranging from 18 to 75 years, (2) status I or II in the Scale of Risk of the American Society of Anaesthesiology, and (3) to have basic computer and mobile phone literacy. Patients were not considered from participation if they had any of following exclusion criteria: (1) A severe physical or mental impairment that precluded the utilisation of the mobile device or the use of the software contained on the device, (2) do not be fluent Portuguese language speakers, or (3) to have previously received cognitive-behaviour therapy (CBT) or (4) to have previously used devices for computerised pain monitoring.

2.3 Study flow

Figure 1 shows the flow diagram, done based on the CONSORT statement recommendations [35], of the progression of participants through the study design. Thirty-seven individuals were assessed for eligibility with five excluded based on the above-mentioned criteria. From these, two had impairment that precluded using the mobile device, one was non-Portuguese speaker and two refused to participate arguing shortage of time. Thus, the participation rate was 86%. The final sample consisted of 32 participants randomly assigned in two groups using a 1:1 ratio: Group I (Intervention Group), including 16 patients submitted to a treatment condition, and Group II (Control Group), including 16 patients not submitted to a treatment condition and used as controls. One participant in group I was lost to follow up due to personal reasons, therefore, our attrition rate was 3,13 %. Both treatment groups continued to receive medical care for their pain condition through a specialty medical clinic. The workflow of this study is shown in Figure 2.

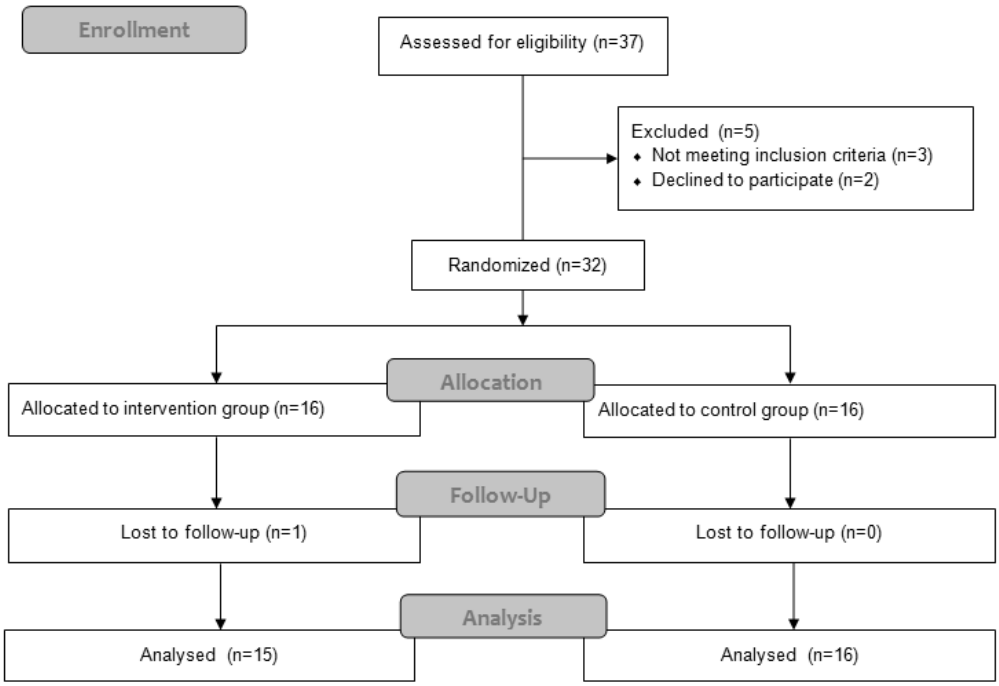

Figure 1: Flow diagram

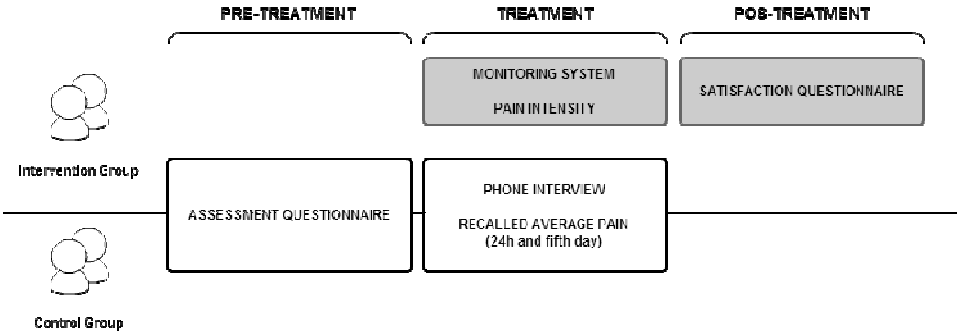

Figure 2: Study workflow

2.4 Assessment

Each patient deemed eligible to participate were asked to complete a informed consent and a battery of assessments in order to obtain baseline values of outcome measures. All patient-reported outcome measures were obtained by asking the participant to complete a seven-point Likert scale questionnaire during hospitalization after surgical intervention and supervised by the HCP. Participants in both arms of the study were called by the HCP after 24 hours and 5 days follow-up and were asked to rate their recalled average pain. During the phone interviews, data were entered directly into the monitoring software. Study personnel assigned to assist participants in the clinic setting were informed about participants' treatment assignment. As part of the computerised monitoring program, participants in this arm of the study complete an additional questionnaire to evaluate his adherence and experience with technology applied to post-operative home based pain monitoring.

2.5 Procedures

A daily electronic pain diary was used to assess self-reported pain of the participant of computerised treatment during the 5-days monitoring period. Participants were asked to complete several pain ratings per day, commonly at morning, afternoon, and evening, in accordance with the treatment protocol. Pain intensity was assessed using an 11-point numerical rating scale (NRS) with anchors of 0 = no pain to 10 = worst pain.

3 TREATMENT CONDITIONS

3.1 Wait-list control group

Participants in the wait-list control group continued with their medical care recommended by their physician, which for all patients involved one-month post-treatment visit at the hospital.

3.2 Computerised treatment group

Participants in the treatment group also continued with their medical care recommended by their physician, and were asked to initiate the 5-days computerised monitoring program, which includes a web-based PHR (Meu Sapo Saúde, provided by PT Comunicações/SAPO, see Figure 3), and a mobile application (app) corresponding to an electronic pain dairy, installed in a smartphone dispensed to every participant in this arm of the study (see Figure 4). Each participant must be registered in PHR.

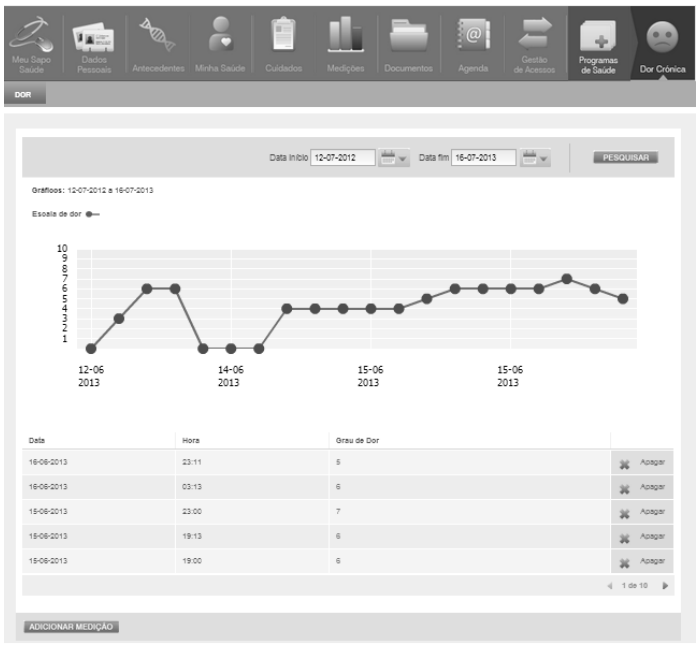

Figure 3: Screen shot of PHR, Meu Sapo Saúde, with histogram showing distribution of pain intensity

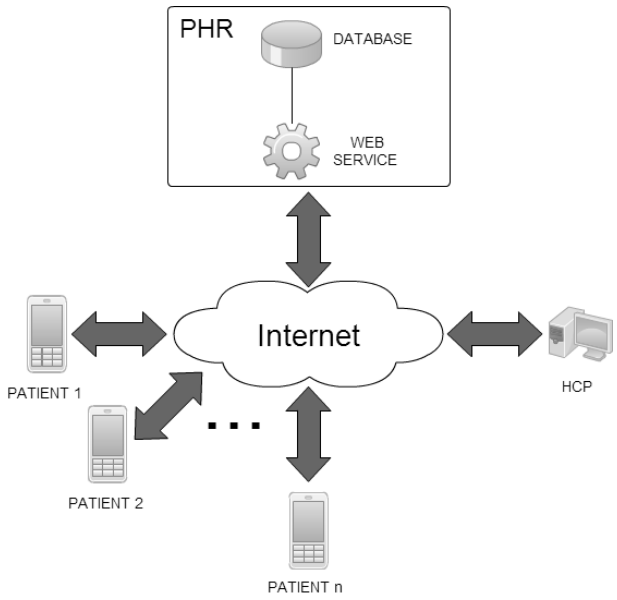

Figure 4: System architecture

The HCP on line access the PHR to define a patient-oriented treatment, in terms of duration, pain record density, medication frequency, rules and subsequent content of auto-generated messages according the collected values and patient symptoms. These rules (IF THEN rules) may differ not only among patients that belong to the same intervention, but also in accordance with monitoring purposes, participants symptoms, and duration of the intervention. Each rule is defined according the structure described below:

IF [pain value] [signal] [value] THEN [message]

where:

- pain value: represents one of the following values: maximum, minimum or mean pain intensity which range between 0 and 10;
- signal: represents a relational operator (e.g. >, <, >=, <=);
- value: represents the reference pain intensity which ranges between 0 and 10;
- message: represents the textual description of the alert.

Each participant is provided by a smartphone which includes an app that periodically, checks for changes in treatment configuration, so as is it always up-to-date according to clinical settings planned by the HCP. Thus, is expected that treatment adjustments along the monitoring process could be more suitable to patient due to the fact that clinical visits are not required. PHR allows to HCP the consultation of obtained data related to each patient, supported by an histogram composed by the pain records.

The app (see Figure 5) remains in background until the scheduled time to taking medication and/or register pain value is verified. In both cases the patient is alerted with an audible alarm. Medication information comprises a textual information whereas the insertion of the momentary value of pain includes a numeric rating scale (NRS) presented to patient over a period of time. Whether this time is exceed, a "no response", represented by a null value, is registered. All obtained values are saved locally, using a SQLite database, and sent to remote PHR via WS, immediately after its recording and then the app return to background. When the communication fails, the value is marked as pending and it is included in the next moment of data transmission. This process is automatic and does not requires patient intervention. In addition, the app allows patient to registered unplanned pain records with identical submission process than the scheduled records. Whenever a message is received, it is saved in the SQLite database, the app is activated and the text is presented to patient. The app activation only occurs during patients' awake time. The collected data are accessible for consultation in the PHR through patient identification composed by username and password. After the treatment period, each patient is asked to return the smartphone to the Hospital.

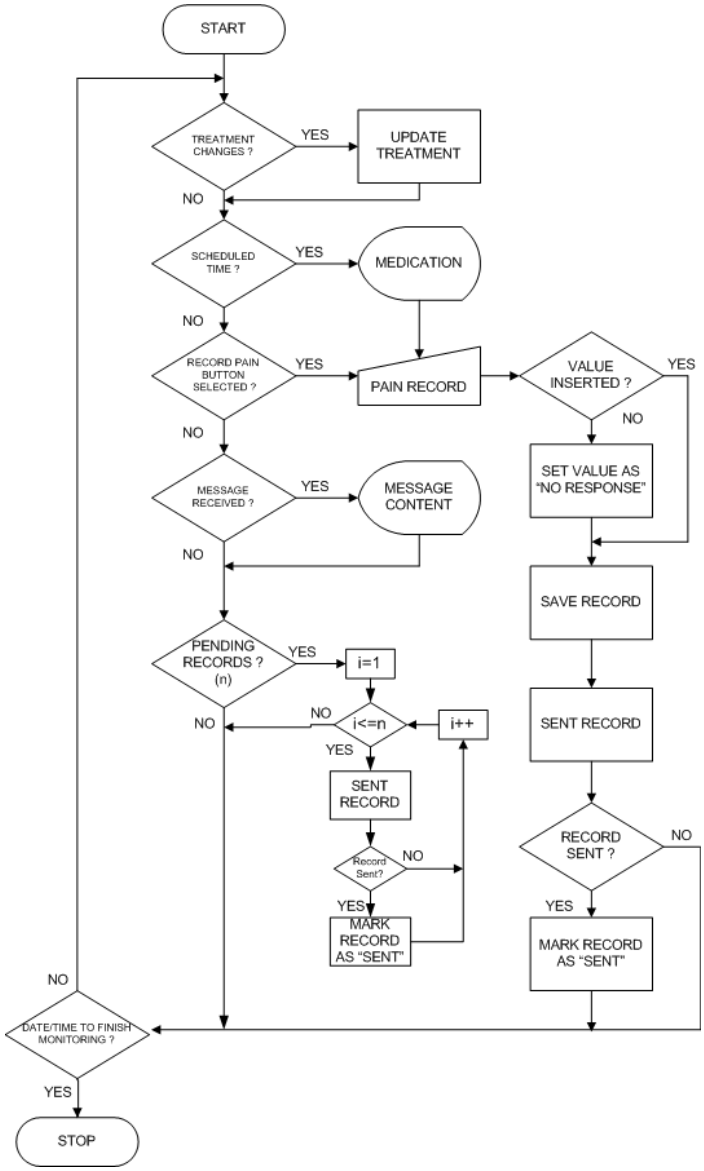

Figure 5: Workflow of the electronic pain diary app

4 STATISTICS

Analyses were done using IBM SPSS 20. Baseline demographic data are expressed in this text as mean and standard-deviation. T-tests assessed differences between the groups despite the use of randomization. Non-parametric data are expressed as median and inter-quartiles range,

comparisons between independent samples performed by Mann-Whitney test and correlations with Spearman's correlation coefficients (r_s).

5 RESULTS

The final sample consisted of 31 patients (14 males and 17 females), aged between 20 and 72. Group I was composed by 15 caucasians patients, 7 female and 8 male, aged 48.07 ± 12.23 years (mean ± SD). Group II was composed by 16 caucasians patients, 10 female and 6 male, aged 50.13 ± 10.79 years. Participants were referred to the treatment study for hand pain (48,4%), followed by pelvic pain (38,7%), knee pain (9,7%), and leg pain (3,2%). Treatment groups were equivalent on age, gender, and race ($p > .05$). Some differences were presented in terms of pain location due to the mixed of acute post-operative pain conditions.

Table 1: Characteristics of the sample combined and by treatment group

Characteristic	Combined Sample (n=31) N(%)/M(SD)	Group I (n=15) N(%)/M(SD)	Group II (n=16) N(%)/M(SD)
Age(years)	49,13 (11,37)	48,07 (12,23)	50,13 (10,79)
Age group			
20-29	3 (9,7%)	2 (13,3%)	1 (6,25%)
30-39	2 (6,5%)	1 (6,7%)	1 (6,25%)
40-49	8 (25,8%)	5 (33,3%)	3 (18,75%)
50-59	14 (45,2%)	6 (40%)	8 (50%)
60-69	3 (9,7%)	0 (0%)	3 (18,75%)
70-75	1 (3,2%)	1 (6,7%)	0 (0%)
Gender			
Male	14 (45,2%)	8 (53,3%)	6 (37,5%)
Female	17 (54,8%)	7 (46,7%)	10 (62,5%)
Race			
Caucasian	31 (100%)	15 (100%)	16 (100%)
Pain Location			
Hand pain	15 (48,4%)	4 (26,7%)	11 (68,75%)
Leg pain	1 (3,2%)	1 (6,7%)	0 (0%)
Knee pain	3 (9,7%)	1 (6,7%)	2 (12,5%)
Pelvic pain	12 (38,7%)	9 (60%)	3 (18,75%)

5.1 RCT of the effects on quality of pain treatment

In the phone call done 24 hours after surgery, Group I presented a median pain intensity of 0 and an inter-quartile range of 2, and Group II respectively 2 and 2. Five days after surgery, the values were 0 and 1 in Group I and 0 and 0 in Group II. As shown in Table 2, despite both groups presented reduction of the pain intensity between 24h and fifth day after surgery, the number of occurrences remained the same in Group I (n=7) whereas it is significantly reduced in Group II (n=2). *T*-test evidences no significant group differences regarding to improvements in the quality of pain treatment ($p = .87$).

Table 2: Recalled average pain

	Group I (n=15) N(%)/M(SD)	Group II (n=16) N(%)/M(SD)
24h recalled pain		
Occurrences	7 (47%)	10 (62,5%)
Average pain intensity when occurred	2,1 (1,06)	2,3 (1,06)
5-days recalled pain		
Occurrences	7 (47%)	2 (12,5%)
Average pain intensity when occurred	1,86 (1,86)	2 (0)

5.2 Compliance to device and user-friendly qualities

The pre-treatment questionnaire (see Table 3) aims at characterising the participants in terms of mobile phone and health services experience and profile. Participants in both arms of the study use regularly mobile phone (Q.1.1, 100/93.3 %) (Question, Group I/Group II %) to make and receive calls (Q.1.2, 100/93.3 %). On the contrary was observed the reduced use of the mobile phone for leisure (Q.1.3, 13.3/6.7 %), professional purposes (Q.1.4, 13.3/0 %) and Internet access (Q.1.5, 13.3/6.7 %) which combination is unsurprisingly greatly correlated ($r_s = .877, p < .01$). In addition, despite the sense of the benefits that may result from use of PHR (Q.2.5, 46.6/60 %) , it knowledge, use and registration (Q.2.1/2/3, 13.3/6.7 %) remains almost inexistent and independent of the patients' age, pain conditions or symptoms.

The analyses of the post-treatment questionnaire (see Table 4 and Table 5) revealed a very strong correlation ($r_s = .844, p < .01$) between the adequate training provided by HCP (Q.3.2) and the ease use of the application (Q.3.1). The adequate training provided by HCP is strong correlated with the suitability of the application to improve pain management (Q.3.9, $r_s = .675, p < .01$), with the recommendation of the application (Q.3.10, $r_s = .750, p < .01$), and with the clearance and the understanding of the terminology used in the application (Q.3.4, $r_s = .626, p < .05$). Moreover, design (Q.3.5) and performance (Q.3.6) presented a very strong correlation ($r_s = .843, p < .01$).

The audibility of the alarm sound (Q.3.7) is strong correlated with the suitability of the application both to provide medical information (Q.3.8, $r_s = .667, p < .01$), and to improve pain management (Q.3.9, $r_s = .695, p < .01$) together with the recommendation of the application ($r_s = .666, p < .01$). In addition, this topic is strong correlated with the suitability of the application to improve pain management ($r_s = .688, p < .01$) and very strong correlated with design (Q.3.3, $r_s = .751, p < .01$) and terminology concepts (Q.3.4 $r_s = .857, p < .01$).

Analysing together the pre-treatment and the post-treatment questionnaires revealed a strong correlation between the ability to use the mobile phone to make and receive calls and the suitability of the application to provide medical information ($r_s = .704, p < .01$) together with the positive effects in the health due to the participation in the study ($r_s = .516, p < .05$).

Based upon all possible records of pain intensity for each subject, the median percent of missed data in the sample was 28% (mean $\pm$ SD 29,6% $\pm$ 11,5%) and the proportion of missed records per participant ranged from 16 to 57,9%. There was no association among gender, age, recalled pain at 24h and fifth day after surgery, and percent missing records (respectively: $r_s = .124, p = .659$, $r_s = .148, p = .600$, $r_s = .339, p = .217$, $r_s = .199, p = .477$).

Table 3: Pre-treatment questionnaire

	Questions
Q.1.1	Do you use the mobile phone regularly?
Q.1.2	Do you use the mobile phone to make / receive calls?
Q.1.3	Do you use the mobile phone to leisure and / or to play games?
Q.1.4	Do you use the mobile phone to run software specific to your professional activity?
Q.1.5	Do you use the mobile phone to access the Internet?
Q.2.1	Do you know about electronic health records, such as: Meu Sapo Saúde or Plataforma de Dados de Saúde?
Q.2.2	Do you subscribe an electronic health record?
Q.2.3	Do you use the electronic health record regularly?
Q.2.4	Do you keep the electronic health record up-to-date?
Q.2.5	Do you consider beneficial the use of the electronic health record?

		1. Mobile phone users' profile N(IG/CG) (IG/CG%)						
		Strongly agree	Agree	Somewhat agree	Neutral	Somewhat disagree	Disagree	Strongly disagree
Q.1.1	Group I	8 (53.3%)	5 (33.3%)	2 (13.3%)				
	Group II	3 (20%)	9 (60%)	2 (13.3%)				1 (6.7%)
Q.1.2	Group I	13 (86.7%)	2 (13.3%)					
	Group II	11 (73.3%)	3 (20%)					1 (6.7%)
Q.1.3	Group I			2 (13.3%)	3 (20%)	1 (6.7%)	3 (20%)	6 (40%)
	Group II			1 (6.7%)			4 (26.7%)	10 (66.7%)
Q.1.4	Group I	1 (6.7%)		1 (6.7%)	1 (6.7%)	1 (6.7%)	3 (20%)	8 (53.3%)
	Group II					1 (6.7%)	1 (6.7%)	13 (86.7%)
Q.1.5	Group I	1 (6.7%)		1 (6.7%)	1 (6.7%)		3 (20%)	9 (60%)
	Group II		1 (6.7%)					14 (93.3%)
		2. Computerised health services users' profile N(IG/CG) (IG/CG%)						
		Strongly agree	Agree	Somewhat agree	Neutral	Somewhat disagree	Disagree	Strongly disagree
Q.2.1	Group I		2 (13.3%)				1 (6.7%)	12 (80%)
	Group II		1 (6.7%)				1 (6.7%)	13 (86.7%)
Q.2.2	Group I		2 (13.3%)				1 (6.7%)	12 (80%)
	Group II	1 (6.7%)						14 (93.3%)
Q.2.3	Group I			2 (13.3%)			1 (6.7%)	12 (80%)
	Group II			1 (6.7%)				14 (93.3%)
Q.2.4	Group I		1 (6.7%)			1 (6.7%)	1 (6.7%)	12 (80%)
	Group II		1 (6.7%)					14 (93.3%)
Q.2.5	Group I	3 (20%)	2 (13.3%)	2 (13.3%)	2 (13.3%)		1 (6.7%)	5 (33.3%)
	Group II	1 (6.7%)	6 (40%)	2 (13.3%)	5 (33.3%)		1 (6.7%)	

Table 4: Pos-treatment questionnaire related to the experience on the usage of monitoring software

	Questions						
Q.3.1	Do you consider that the application is easy to use?						
Q.3.2	Do you consider that the training provided by the HCP was suitable?						
Q.3.3	Do you consider that the application presents an attractive design?						
Q.3.4	Do you consider that the terminology is clear and understandable?						
Q.3.5	Do you consider that the font colour and size are easy to read on screen?						
Q.3.6	Do you consider that the response time of the application is fast enough?						
Q.3.7	Do you consider that the alarm sound is easily audible?						
Q.3.8	Do you consider that the application is suitable to access to the medical indications?						
Q.3.9	Do you consider that the application is suitable to improve the management of post-operative pain?						
Q.3.10	Do you recommend the application?						
	N (%)						
	Strongly agree	Agree	Somewhat agree	Neutral	Somewhat disagree	Disagree	Strongly disagree
Q.3.1	6 (40%)	6 (40%)	2 (13.3%)	1 (6.7%)			
Q.3.2	7 (46.7%)	8 (53.3%)					
Q.3.3	4 (26.7%)	10 (66.7%)	1 (6.7%)				
Q.3.4	6 (40%)	7 (46.7%)	2 (13.3%)				
Q.3.5	4 (26.7%)	10 (66.7%)	1 (6.7%)				
Q.3.6	4 (26.7%)	6 (40%)	3 (20%)		1 (6.7%)		1 (6.7%)
Q.3.7	7 (46.7%)	5 (33.3%)	1 (6.7%)				2 (13.3%)
Q.3.8	2 (13.3%)	10 (66.7%)		1 (6.7%)	1 (6.7%)		1 (6.7%)
Q.3.9	3 (20%)	8 (53.3%)	1 (6.7%)	2 (13.3%)			1 (6.7%)
Q.3.10	5 (33.3%)	9 (60%)	1 (6.7%)				

Table 5: Pos-treatment questionnaire related to the experience on the study participation

	Questions						
Q.4.1	Do you consider that the information provided on this study was sufficient and enlightening?						
Q.4.2	Do you consider that participating in the study was beneficial to improve your health?						
Q.4.3.	Do you consider that participating in the study enabled a faster access to information?						
Q.4.4.	Do you consider that participating in the study contributed to reduce the costs associated with treatment?						
	N (%)						
	Strongly agree	Agree	Somewhat agree	Neutral	Somewhat disagree	Disagree	Strongly disagree
Q.4.1	6 (40%)	7 (46.7%)	1 (6.7%)		1 (6.7%)		
Q.4.2	4 (26.7%)	8 (53.3%)	1 (6.7%)	1 (6.7%)		1 (6.7%)	
Q.4.3.	1 (6.7%)	11 (73.3%)	2 (13.3%)			1 (6.7%)	
Q.4.4.	2 (13.3%)	4 (26.7%)	3 (20%)	5 (33.3%)		1 (6.7%)	

6 DISCUSSIONS AND CONCLUSIONS

Our study proved that the system tested which combines a web-based PHR and mobile devices is feasible and patients are compliant to it and considered the device as user-friendly. Our findings extend previous work on pain monitoring [21,25,35–40] demonstrating its acceptability, satisfaction, and compliance with computerised treatment among patients with mixed acute pain conditions. Looking specifically to the device created by us, a majority of participants recommend the system and recognize that it is appropriate for pain management, and is user-friendly, not requiring advanced skills nor experienced users.

These findings are even more significant since participants are chiefly middle aged and presented a high illiteracy in terms of handling applications on mobile devices and/or Internet access. Another strength of the current study was to provide the evaluating of a purely mobile and web-based, no-contact intervention for use in the context of routine care. Such a no-contact intervention holds the advantage of being broadly available which may be critical to providing access to a large number of patients. The pain monitoring system could have major implications if accessed more widely so as to enhance the potential societal benefits in terms of pain management and well-being [36].

Furthermore, the inclusion of PHR in the monitoring system enabled reliable message delivery required for emergency messages in a fully automated fashion and scalability to support as many patients as possible, with online persistent data available to patient and HCP. The PHR revealed it suitability to pain monitoring, providing ubiquitous and real-time access and allowed an effortless definition and management of patient-oriented treatment rules with minimal therapist. The guidance of HCP at the beginning of the monitoring is crucial to patients' satisfaction and experience stemming from the usage of the system as evidenced by the high correlation between the recommendation of the application, and it suitability to improve pain management and to provide medical information. The absence of detected and reported errors related either to the app or to the PHR, suggest that the proposed system is stable and reliable. Due to the fact that the electronic pain diary is based on periodical alarms in accordance with the medical protocol, the audibility of the alarm sound is crucial to the system adherence and accuracy. The percent of missed data in the sample was 29,6% ± 11,5%, essentially due to the fact that participant did not hear the alarm or it occurred at inconvenient time.

Concerning our aim to evaluate how much our system increase the quality of pain treatment in ambulatory surgery, our RCT fails to prove any difference between groups. Explanation can be done based on the small scores of pain registered in both groups, even at 24 hours after the surgical procedure. Reasons for these low scores are that for inclusion in this preliminary study we choose relative minor surgical interventions and usual protocols of the Ambulatory Department, maintained unchangeable during all study, aimed to maintain patients without pain, even without any kind of monitoring or regular accompaniment. Detection of differences concerning quality of pain treatment in ambulatory surgery probably imposed the use of major surgery.

The system with minor differences in software in also created for monitoring in chronic pain, including oncology claims. Further studies are also necessary to evaluate the ability to increase quality of treatments in these clinical areas where pain is frequently a problem of difficult resolution. In addition, future studies should be addressed to determine the economic effects of the proposed monitoring model not only to patients but also to the healthcare system. Moreover

further work is needed to evaluate the proposed system to follow up participants for longer periods of time which includes a complementary randomised controlled trial encompassing patients with chronic pain symptoms.

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Chapter 7

Design and Evaluation of a Decision Support System for Pain Management Based on Data Imputation and Statistical Models

This chapter consists of the following article:

Design and Evaluation of a Decision Support System for Pain Management Based on Data Imputation and Statistical Models
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Design and Evaluation of a Decision Support System for Pain Management Based on Data Imputation and Statistical Models

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ABSTRACT

The self-reporting of pain complaints is considered the most accurate pain assessment method and represents a valuable source of data to computerised clinical decision support systems (CCDSS) for pain management. However, the subjectivity and variability of pain conditions combined with missing data are constraints to useful and accurate CCDSS. Based on data imputation principles together with several statistical models this paper presents a CCDSS, called Patient Oriented Method of Pain Evaluation System (POMPES) so as to produce tailored alarms, reports, and clinical guidance based on collected patient-reported data. This system was tested using clinical data collected during a six weeks randomised controlled trial evolving thirty-two volunteers recruited in an ambulatory surgery department. The decisions resulted from POMPES were fully accurate when compared with the medical advices which proved the ability to deal with missing data and to detect either the stability or change in the self-reporting of pain.

Keywords: clinical decision support system, post-operative, pain assessment, data imputation, linear regression, analysis of variance.

1 INTRODUCTION

In the last years, computerised clinical decision support systems (CCDSS) were largely used to enhance health, affords health care professionals (HCP) and patients with knowledge and individualised information, intelligently selected or presented at appropriate times. These systems may lead to a better clinical guidance, patients' perspective of their condition, and HCP' practices [1–5], established on decisions taken not only on the basis of their perception and experience, but also supported on the collected data. In addition, automated alerts, reminders, availability of information when and where it is needed, are features intended to optimize the clinical workflow [6,7], and thus improve the quality of treatment. When this occurs, is considered that the computerised system represents a support to medical decisions instead a merely stand-alone software that is designed to operate in parallel to HCP. Thus, design CCDSS models to represent medical concepts and tasks, such as diagnosis, treatment, or screening, poses several challenges so as to result in systems with capability to make better use of the existing data and to extend the information on which decisions are based. Moreover, the problem of missing values commonly arises in the collected data [8,9] that are processed by the CCDSS which may lead to incorrect and inaccurate analyses.

In line with this, mathematical models were increasingly adopted by the CCDSS aiming to enhance the data analysis and processing so as to produce patient-oriented recommendations that are delivered to HCP [10–12]. Furthermore, several techniques of data imputation were developed to compensate the missing data [13] which aiming to allow more precise and reliable systems. These improvements related to CCDSS are even more significant when these systems are applied to manage patient-specific conditions with large variability and harder assessment, such as pain symptoms. In fact, the subjectivity of pain relies of physiological, neurological and psychological aspects representing a multidimensional experience [14–18] that raises several challenges to the definition of right treatments [19]. In addition, since the self-reporting of pain complaints is considered the most accurate pain assessment method [20–22], these data are of particular importance to the reliability of CCDSS applied to pain management and therefore is critical to solve the existence of gaps in the data set.

The aim of this study is to present and validate a CCDSS, called Patient Oriented Method of Pain Evaluation System (POMPES), which comprises data imputation principles and adaptable statistical models so as to produce tailored alarms, reports, and clinical guidance based on collected patient-reported data. The paper is organized as follows. Section 2 presents the state-of-the-art focusing on data imputation techniques and algorithms used by CCDSS, whereas Section 3 addresses the monitoring system in which the proposed decision model was applied and tested. Section 4 presents a detailed explanation of mathematical concepts behind the system which results are present in Section 5. Finally, Section 6 concludes the paper.

2 BACKGROUND

In this study, the existing algorithms used by CCDSS applied to pain measurement were categorised into the following topics: rule based algorithms (RBA), artificial neural networks (ANN), rough and fuzzy sets (RFS), and statistical learning algorithms (SLA).

- RBA [23–30], comprised decision tree algorithms, such as ID3 [31], C4.5 [32], CN2 [33], and algorithms that aims to optimize and/or ranking of decision rules and variables, namely CART [34], ITRULE [35] and ILLM [36]. RBA produce understanding classifications, nevertheless some limitations are present, such as the overspecialisation or the inability for learning from incomplete data [37–39].

- ANN [40–51], generate an output set where each element represents a particular classification for the input set. This is achieved via the propagation of estimated weights through the nodes of the network obtained from a batch of training, in a repeated way. ANN presents robustness to noisy data and ability to represent complex functions [52,53], whereas the inability to explain decision, to present data clearly [38,54], and to determine the adequate size of the hidden layer (when multiple layers are used) are disadvantages observed [55,56].

- RFS [57–68] is composed by rough set [69] and fuzzy set [70] models. The rough set is obtained from the difference between two sets of elements: those that certainly belong to the set and those that probably belong to the set. This algorithm does not require additional information about data, however tend to be noisy and unsuitable for large data sets [71,72]. On the contrary, fuzzy set represents a probabilistic logic model that uses reasoning to explain whether an event is about to happen, which means that every element within the set has a degree of relevance (a.k.a. membership) varying between 0 (or false) and 1 (or true). Thus, it is suitable to represent uncertain or flexible information [73], despite its difficulty to estimate the membership functions [74].

- SLA [75–85], encompass Bayes' theorem (a.k.a. Bayes' rule) [86], naive Bayes [87], Bayesian network [88], logistic regression (LR) [89], and support vector machine (SVM) [90]. Bayesian algorithms are time-consuming models and required a thorough knowledge of its parameters [91,92]. LR is less susceptible to overfitting [93], however is unsuitability to deal with non-linear problems [94]. SVM has good generalisation ability, but it is very sensitive to uncertainties [52], and a too high dimensional space can lead to overfitting of the data [53,95]. Furthermore, a subset of SLA related to statistical models may also be considered due to the fact that they are largely used to comparison of the collected data, estimating treatment effects, assess outcomes and consequently to determine the accuracy and validity of computerised systems applied to pain measurement. These models were presented by several authors differing from the Fisher's test [96,97], Pearson's test [96,98–100], and *t*-test [97,101–106] to methods based on the analysis of variance and covariance such as: ANOVA [100,107–115], ANCOVA [116–118], MANOVA [104,112,119] or MANCOVA [120].

Regardless the selection of the appropriate algorithm, the conception of CCDSS for pain management faces an additional challenge related to the missing of data. In this study, the existing techniques to deal with missing data were categorised into the following topics:

- Deletion Methods [121,122]: consists either of discarding all records with missing values for at least one variable (listwise deletion) or discarding only instances with missing values for the less important variables (pairwise deletion). Simplicity is the main advantage whereas the reduction of the statistical power and inability to compare analysis (when pairwise deletion is used) are limitations.
- Simple Methods [123–127]: consists of replacing missing data with computed values estimators (mean, median, mode, hot-deck, ...) or applying regression imputation such as linear, multiple linear and logistic regression. The hot-deck imputation estimates missing values on incomplete records using values from similar complete records. This model may reduce the bias of the complete case analysis, however lead to bias in multi-variance analysis. The adoption of imputation estimators based on mean, median or mode is likely to reduce the variability of data. Moreover, mean imputation is affected by the presence of outliers, for that reason in some cases the median imputation is more appropriate, and may create spikes in the distribution of the data. The regression imputation replaces missing data based on cases with complete data. This technique may reduce the problem of spikes, however it may overestimate the model fit and weaken the variance.

- Model-based Methods [124,128–134]: consists of replacing missing data with more sophisticated models such as maximum likelihood, multiple imputation and machine learning techniques such as SVM or ANN. Maximum likelihood estimated the missing data using a set of records that is most likely to have resulted in the observed data. Multiple imputation uses a model to replace missing data multiple times. The main difficulty lies in designing a suitable method to perform the imputation [135] (Monte Carlo Markov Chain and Multiple Imputation by Chained Equations are often used). Maximum likelihood and multiple imputation may produce unbiased estimates. The Nearest-neighbour imputation determines the similarity of two records using a distance between them. This method can deal with records with multiple missing values and considers the correlation structure of data [136]. However, the time consuming and the choose of the distance function are limitations.

3 MONITORING SYSTEM

The proposed CCDSS aims to support HCP during the monitoring of patients suffering with pain, independently of their conditions and self-reporting frequency and is validated using a computerised pain monitoring system [137] developed by our research team. As shown in Figure 1, the proposed system is running on server-side and integrated with a Personal Health Record (PHR) accessible to HCP and patients. The input set of this system is based on patients' self-report data inserted directly on the PHR using a browser or collected via mobile device and sent to the PHR using web services (WS). At last, the monitoring software combines the outcome provided by the CCDSS with the patients' monitoring rules (e.g. value-oriented messages) defined in the PHR so as to produce alarms and alerts messages to either HCP or patients.

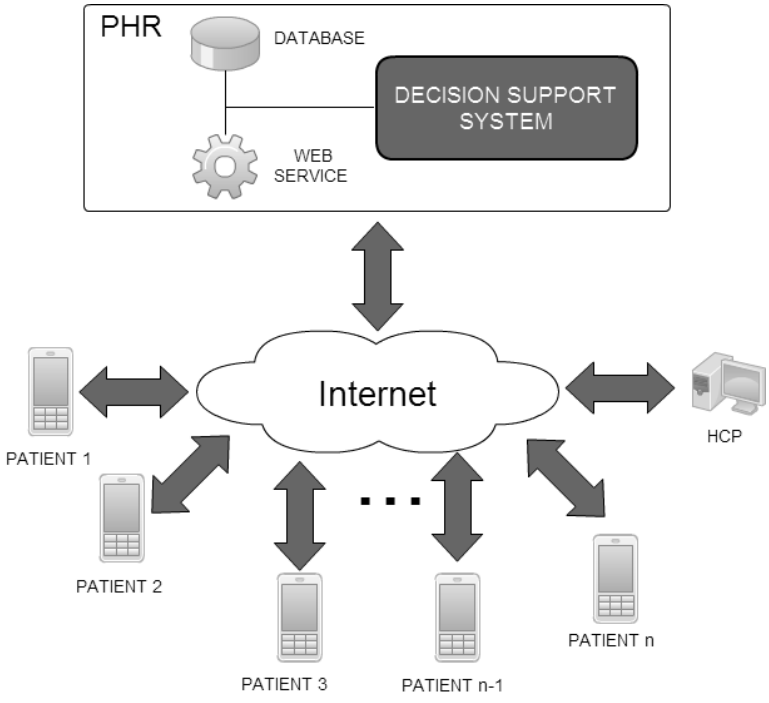

Figure 1: System architecture

4 METHODS

Since the proposed CCDSS aims to support HCP during the monitoring of patients suffering with pain, some topics should be ensured. First, the system should be able to estimate values to appropriately replace the values missing in a data set. Second, the system should be able to determine either stability or change in pain intensity obtained from the self-reporting. Third, when changes occur, the system should be able to present whether it represents a favourable or unfavourable evolution. Thus as shown in Figure 2, the decision model encompasses the following components: input, data imputation, analysis of variance, discrepancy analysis, and output.

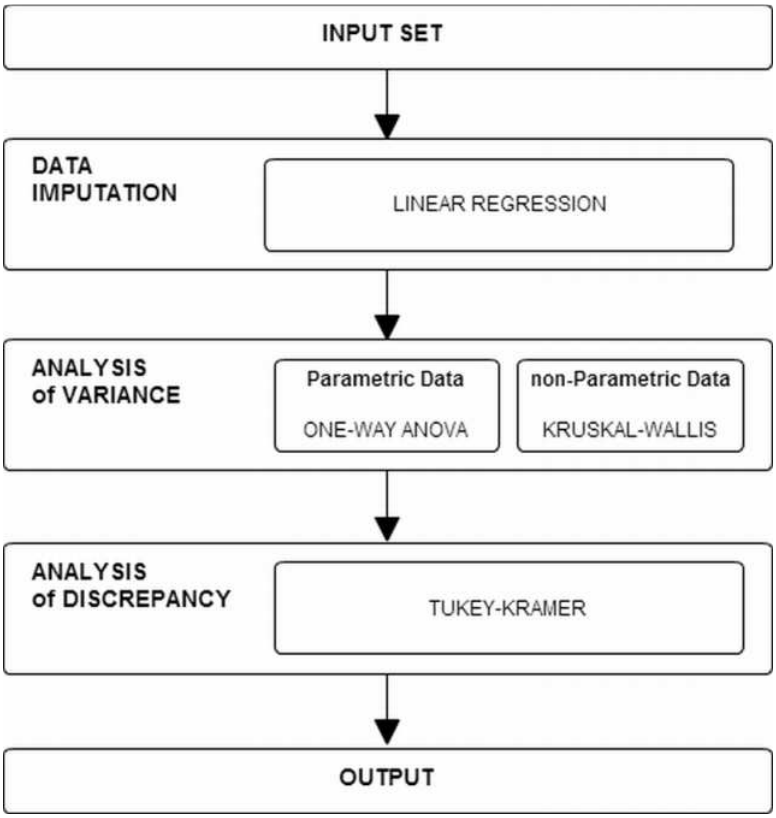

Figure 2: Decision workflow

The input is adjusted in accordance with the treatment protocol and duration of the monitoring which may express different granularities. Therefore, the entire pain intensity records are sectioning into *k* elements representing different treatment periods that may express from several records to several days. All the missing records were determined using a linear regression model based on the least squares estimation.

To ensure the generality of the proposed system the analysis of variance is based on the one-way ANOVA model whenever data are parametric, or Kruskal-Wallis otherwise. The discrepancy analysis is determined based on the Tukey-Kramer principles so as to compare the several elements that compose the input. At last, the output includes whether variance is determined (true or false), the qualitative analysis resulted from the comparisons among the multiple treatment periods which is computed whenever the variance occurs. Moreover, the output is complemented with the maximum, minimum, mean pain intensity of each treatment period, elapsed time and number of missing responses since the last inserted record.

It should be noted that some parameters included in the output represent input values to the patients' monitoring rules (IF THEN rules) defined in the PHR. In fact, the obtained maximum, minimum and mean pain intensity may give rise to the emission of alert messages to either patients or HCP. The PHR enables the HCP to configure unlimited combination of rules according the structure described below:

IF [pain value] [signal] [value] THEN [message]

where:

- pain value: represents one of the following values: maximum, minimum or mean pain intensity which range between 0 and 10;
- signal: represents a relational operator (e.g. >, <, >=, <=);
- value: represents the reference pain intensity which ranges between 0 and 10;
- message: represents the textual description of the alert.

4.1. Data Imputation

The data imputation was determined using a linear regression based on a least-squares estimation as defined below.

Given the data pairs (x_i, y_i), for $i = 1, 2, ..n$ observations, then

$y_i = f(x_i; \beta)$, where β is the regression parameters vector and f is a linear function (1)

The predictor of y is obtained by:

$$\hat{y} = \beta_0 + \beta_1 x \tag{2}$$

This equation state if y and x could be measured with no errors in either x_i or y_i, they would be exactly related. Usually, it is assumed that x_i is known exactly and y_i is observed with error.

The β_0 and β_1 are obtained by:

$$\beta_1 = \frac{n\sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i \sum_{i=1}^{n} y_i}{\sqrt{(n\sum_{i=1}^{n} x_i^2 - (\sum_{i=1}^{n} x_i)^2)(n\sum_{i=1}^{n} y_i^2 - (\sum_{i=1}^{n} y_i)^2)}} \left(\frac{SD_y}{SD_x} \right) \tag{3}$$

$$\beta_0 = \overline{Y} - \beta_1 \overline{X} \tag{4}$$

where $\overline{Y}$ and $\overline{X}$ are the means of y and x respectively. Finally SD_y is the standard deviation of y and SD_x is the standard deviation of x.

4.2. Analysis of Variance

Whenever the input set represents parametric data, the analysis of variance is based on the one-way ANOVA as defined below.

We can formulate a statistical hypothesis test to look for differences among means. The null hypothesis is:

$$H_0 : \mu_1 = \mu_2 = \ldots = \mu_k, \text{ for } k \text{ treatment periods} \quad (5)$$

which represents the assertion that all of the means (treatment periods) are the same, stating that patients conditions outcomes are stable during the considered monitoring period.

The alternative hypothesis, that represents differences among the means is:

$H_1 : \mu_i \neq \mu_j$, for some $i \neq j$, where $\mu_1, \mu_2, \ldots, \mu_k$ are the means of k treatment periods (6)

The overall mean (a.k.a. grand mean) is the mean of the k means $\mu_1, \mu_2, \ldots, \mu_k$ and is obtained by:

$$\overline{\overline{X}} = \frac{1}{N}\left(\sum_{j=1}^{k}\sum_{i=1}^{n} X_{ij}\right) \quad (7)$$

where k is the number of treatment periods, n is the number of samples of the j-treatment period and $\boldsymbol{N}$ represents all observations.

The total sum of squares is obtained by:

$$SS_T = \sum_{j=1}^{k}\sum_{i=1}^{n}(X_{ij} - \overline{\overline{X}})^2 \quad (8)$$

where $\overline{\overline{X}}$ is the grand mean, k is the number of treatment periods, and n is the number of samples of the j-treatment period.

The within-sample variation is the average of the all the variances for each treatment period and is obtained by:

$$SS_W = \sum_{j=1}^{k}\sum_{i=1}^{n}(X_{ij} - \overline{X}_j)^2 \quad (9)$$

where $\overline{X}_j$ is the mean of the *j*-treatment period, *k* is the number of treatment periods, and *n* is the number of samples of the *j*-treatment period.

The between-sample variation (a.k.a. error) is the square variations of each treatment period mean minus the overall mean, obtained from the total of all the data values divided by the total sample size:

$$SS_B = \sum_{j=1}^{k} n_j (\overline{X}_j - \overline{\overline{X}})^2 \tag{10}$$

where n_j is the number of samples of the *j*-treatment period, $\overline{X}_j$ is the mean of the *j*-treatment period, and $\overline{\overline{X}}$ is the grand mean.

The within-sample variation, between-sample variation and the total sum of squares are related by:

$$SS_T = SS_B + SS_W \tag{11}$$

The statistical technique used in this case is known as one-way ANOVA, which it is also called by F-test, because the calculation results in a number (called, in general, a test statistic) denoted by F [138]. The decision is made to either reject or not reject the overall null hypothesis in accordance with the comparison between the obtained value of F and the tabulated values resulting from the Fisher-Snedecor distribution (a.k.a. $F_{tabulated}$) with $\alpha = 0.05$.

$$F_{test} = \frac{Between-sample\,estimate}{Within-sample\,estimate} = \frac{\frac{SS_B}{(k-1)}}{\frac{SS_w}{(N-k)}} \tag{12}$$

where *k* is the number of treatment periods, and ***N*** represents all observations.

When the null hypothesis is rejected, as defined in (6), the inference made is that there is some difference among the means, representing discrepancies in patients' conditions.

Since the input set represents non-parametric data, the system computed the analysis of variance based on the Kruskal-Wallis [139] model as defined below.

The Kruskal-Wallis test which is a non-parametric test equivalent to the one-way ANOVA and a generalization of the Wilcoxon test for two independent samples [140]. This model assumes the null and alternative hypothesis as defined in (5) and (6) respectively.
All observations, given by:

$$\sum_{j=1}^{k} n_j = N \tag{13}$$

where j=1, ..., k independent treatment periods, and n_j is the number of the samples of the j-treatment period, are ranked together from lowest to highest. Then the Kruskal-Wallis H statistic is based on the sum of the ranks for each treatment period:

$$H = \frac{12}{N(N+1)} \sum_{j=1}^{k} \frac{R_i^2}{n_j} - 3(N+1) \tag{14}$$

where j=1, ..., k independent treatment periods, R_i represents the i-rank, n_j is the number of the samples of the j-treatment period, and N represents all observation.

The decision is made to either reject or not reject the overall null hypothesis in accordance with the comparison between the obtained value of H and the Chi-square distribution (χ^2) with degree of freedom $df = k - 1$ and $\alpha = 0.05$. So, the null hypothesis is rejected if the observed value of H equals or exceeds this value.

4.3. Discrepancy Analysis

Finally, when the null hypothesis is rejected then the trend regarding to the different input sets is calculated, so as to ascertain variations in the patients symptoms which are directly related with the reported pain intensity. The Tukey-Kramer principles was applied to compare multiple treatment periods so as to detect changes among them and therefore determine the reduction or increase of the reported pain intensity. The reduction suggests positive effects caused by the treatment while the opposite means decline on patients' health and welfare. This analysis is extremely important because it may enable the system to produce oriented messages to HCP

and patients based on the outcome obtained from the multiple comparisons among treatment periods.

The absolute difference between the i and $j-$ treatment periods is given by:

$$abs(\text{sum of } n_i \text{ - sum of } n_j) \tag{15}$$

where n_i , n_j are the observation values of *i* and *j*-treatment periods.

The confidence interval for comparisons is calculated using the formula:

$$\bar{y}_i - \bar{y}_j \pm q_{\propto,v,k}\sqrt{\frac{\sum_{m=1}^{k}\sum_{l=1}^{n}(X_{lm} - \overline{X}_m)^2/(N-k)}{2}\left(\frac{1}{n_i}+\frac{1}{n_j}\right)} \tag{16}$$

where n_i , n_j are the sample size of *i* and *j*-treatment periods, *v* is the degree of freedom, $\overline{X}_m$ is the mean of the *m*-treatment period, *k* is the number of treatment periods, *n* is the number of samples of the *m*-treatment period, and *N* represents all observations.

The critical range between the *i* and *j*-treatment periods is given by the multiplication of (16) with the *Q* statistic value with degree of freedom: $df = N - k$ and $\alpha = 0.05$.
At last, whether the absolute difference is greater than the critical range then i and $j-$ treatment periods exhibit differences.

The proposed decision support model resulted in the algorithm described below:
Step 1. Input processing: the patient data set is sectioning into k treatment periods
Step 2. IF missing value THEN

Computes elapsed time since the last inserted record and the number of missing records

GO TO Step 6

ELSE IF pending missing records THEN

Data imputation using Linear Regression

Step 3. IF data represents a normal distribution THEN

Analysis of variance using ANOVA

ELSE

Analysis of variance using Kruskal-Wallis

Step 4. IF analysis of variance represents a significant difference THEN

Analysis of Discrepancy using Tukey-Kramer

Step 5. Computes maximum, minimum and mean of pain intensity

Step 6. Output processing

5 RESULTS

The data were collected during a six weeks randomised controlled trial (RCT) conducted at the Hospital Sousa Martins in Guarda, Portugal. The final sample consisted of 32 patients (see Figure 3) which baseline demographic and clinical status are detailed in Table 1. The patients' age varied from 18 to 75 years old. Participants presented acute pain resulting from surgical intervention and were recruited through specialty care physician referral from the Ambulatory Surgery Department. The protocol of the study was approved by the appropriate Ethics Committee, and the participants were enrolled after written informed consent. A daily electronic pain diary, installed in a smartphone dispensed to every participant of the intervention group, was used to assess self-reported pain during the 5-days monitoring period. Participants were asked to complete several pain ratings per according the protocol treatment selected for each patient. Pain intensity was assessed using an 11-point numerical rating scale (NRS) with anchors of 0 = no pain to 10 = worst pain. Participants in both arms of the study were called by the HCP after 24 hours and 5 days follow-up and were asked to rate their recalled average pain. Based upon all possible records of pain intensity for each subject, the median percent of missed data in the sample was 28% (mean $\pm$ SD 29,6% $\pm$ 11,5%) and the proportion of missed records per participant ranged from 16 to 57,9%. There was no association among gender, age, recalled pain at 24h and fifth day after surgery, and percent

missing records (Spearman's rank respectively: $r_s = .124, p = .659$, $r_s = .148, p = .600$, $r_s = .339, p = .217$, $r_s = .199, p = .477$).

Table 1: Characteristics of the sample combine and by treatment group

Characteristic	Combined Sample (n=31) N(%)/M(SD)	Group I (n=15) N(%)/M(SD)	Group II (n=16) N(%)/M(SD)
Age(years)	49,13 (11,37)	48,07 (12,23)	50,13 (10,79)
Age group			
20-29	3 (9,7%)	2 (13,3%)	1 (6,25%)
30-39	2 (6,5%)	1 (6,7%)	1 (6,25%)
40-49	8 (25,8%)	5 (33,3%)	3 (18,75%)
50-59	14 (45,2%)	6 (40%)	8 (50%)
60-69	3 (9,7%)	0 (0%)	3 (18,75%)
70-75	1 (3,2%)	1 (6,7%)	0 (0%)
Gender			
Male	14 (45,2%)	8 (53,3%)	6 (37,5%)
Female	17 (54,8%)	7 (46,7%)	10 (62,5%)
Race			
Caucasian	31 (100%)	15 (100%)	16 (100%)
Pain Location			
Hand pain	15 (48,4%)	4 (26,7%)	11 (68,75%)
Leg pain	1 (3,2%)	1 (6,7%)	0 (0%)
Knee pain	3 (9,7%)	1 (6,7%)	2 (12,5%)
Pelvic pain	12 (38,7%)	9 (60%)	3 (18,75%)

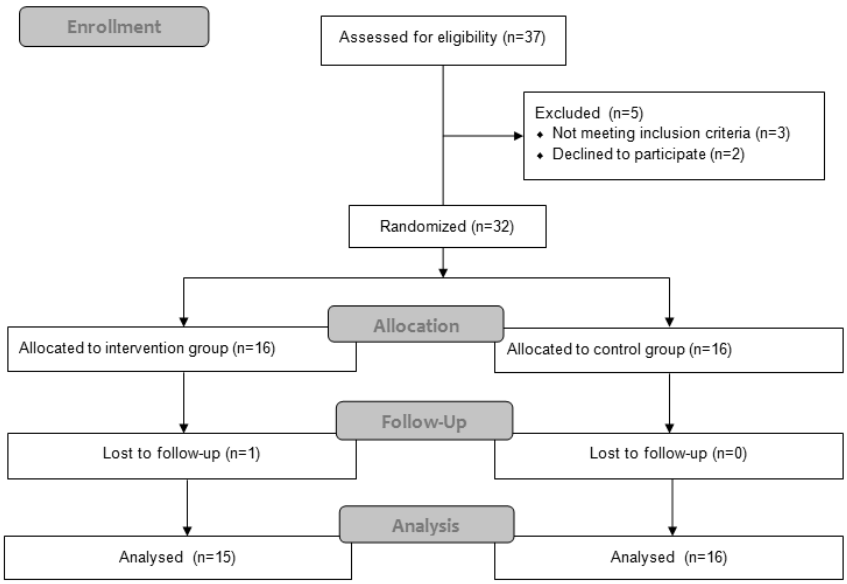

Figure 3: RCT flow diagram

The decision support system flow during the 5-days monitoring period is shown in Table 2 which includes a representative data set of both situations related with pain complaints, namely the standard case which occurs when pain remains stable and less intense and the exceptional case when pain intensity is high or presents fluctuations (increasing or decreasing). This data set is related to a patient that was asked to rate his pain severity six times a day which leads to an individual sample of 30 records. Due to the fact that these data are significantly deviate from a normal distribution (Shapiro-Wilk test, $p < .05$) the analysis of variance was computed using the Kruskal-Wallis model.

The system requires at least two records to begins the data analysis. Thus, in S2, the data set [0,3] is divided into two groups and the Kruskal-Wallis test is computed revealing the inexistence of variance between the two groups ($p > .05$). In S3-S7 only the time lapse since the last inserted record and the number of missing records are computed due to the fact that values are missing. Since S8 is the first occurrence of an inserted value after missing values the system processes the data imputation, using a linear regression model which obtained values are rounded to the nearest integer which resulted in the following data set: [2, 3, 3, 4, 5]. Then, the Kruskal-Wallis test includes these imputation values revealing significantly variance between the groups. The group 1 and group 2 are composed respectively by [0, 3, 2, 3] and [3, 4, 5, 6] which evidenced significantly changes of the patient conditions.

In addition, the analysis of discrepancy is calculated using Tukey-Kramer model. Between S9 and S26 is considered that pain conditions are stable (Kruskal-Wallis test resulted in $p > .05$). At last in S27 and S30 a significantly variance is obtained which represents a higher difference between the fifth day of monitoring and the previous days. In S8, S10, S13, S20, S25 and S30 the data imputation is computed.

Table 2: Decision support system flow during 5-days monitoring period

S	Value	Regression Value	Kruskal-Wallis			Tukey-Kramer Calculation	Comments
			Groups	χ^2	p -value		
1	0						
2	3		1/1	1	0,317		p>0,05 null hypothesis accepted
3	X	3					
4	X	3					
5	X	4					
6	X	5					
7	X	5					
8	6		4/4	5,671	0,017	Yes	Linear regression calculated, p<0,05 null hypothesis rejected
9	X	4					
10	0		5/5	2,563	0,109		Linear regression calculated, p>0,05 null hypothesis accepted
11	0		6/5	0,140	0,709		p>0,05 null hypothesis accepted
12	X	3					
13	4		6/6/1	0,394	0,821		Linear regression calculated, p>0,05 null hypothesis accepted
14	0		6/6/2	0,282	0,868		p>0,05 null hypothesis accepted
15	4		6/6/3	0,095	0,954		p>0,05 null hypothesis accepted
16	4		6/6/4	0,154	0,926		p>0,05 null hypothesis accepted
17	5		6/6/5	0,501	0,778		p>0,05 null hypothesis accepted
18	X	2					
19	X	2					
20	0		6/6/6/2	1,830	0,608		Linear regression calculated, p>0,05 null hypothesis accepted
21	0		6/6/6/3	3,208	0,361		p>0,05 null hypothesis accepted
22	0		6/6/6/4	4,535	0,209		p>0,05 null hypothesis accepted
23	0		6/6/6/5	5,799	0,122		p>0,05 null hypothesis accepted
24	X	1					
25	0		6/6/6/6/1	7,405	0,116		Linear regression calculated, p>0,05 null hypothesis accepted
26	0		6/6/6/6/2	8,557	0,073		p>0,05 null hypothesis accepted
27	0		6/6/6/6/3	9,661	0,047	Yes	p<0,05 null hypothesis rejected
28	X	0					
29	X	0					
30	0		6/6/6/6/6	12,757	0,013	Yes	Linear regression calculated, p<0,05 null hypothesis rejected

Legend:	**S**: sequential order of inserted records
	Value: inserted pain intensity value [0..10]. **X** for missing records.
	Regression Value: value (rounded to the nearest integer) obtained from linear regression
	Groups: Combination of record to compose Kruskal-Wallis' and Tukey-Kramer's groups.
	(Number of records of Group 1/ Number of records of Group 2/..../ Number of records of Group 5)
	χ^2, p -value: Kruskal-Wallis calculation
	Tukey-Kramer calculation: indicates whenever the Tukey-Kramer is computed
	Comments: additional information

6 DISCUSSIONS AND CONCLUSIONS

The lack of correlation among gender, age, recalled pain and percent missing records suggests that data were missing completely at random (a.k.a. MCAR), therefore not dependent of patients' profile neither pain conditions.

The proposed system revealed to be suitable to detect changes in patients' conditions as verified in S8 which was observed deterioration of pain. Thus, the information provided to HCP in S8 was useful and timely report about the patient condition so as to support the decision of treatment adjustments. In addition, a measurement of the obtained variance was provided to HCP using the Tukey-Kramer model.

Moreover, the stability of pain conditions was also detected by the system as evidenced by the computed values between S9 and S26. In spite of the observed reduction of pain intensity after S20 its differences are not statistical significant until S27. However, the system so as to provide to HCP a complete information about the collected data also includes the maximum, minimum and the calculated mean related to pain intensity reported each day. Thus before S27, the system provided the required information to HCP so as to support clinical decisions with data which evidencing the favourable evolution of the patient condition.

The preliminary results evidenced the proposed system called POMPES is suitable for acute pain management as evidenced by the accuracy of diagnosis as consequence of its ability to detect stability (standard case) or change (exceptional case) in pain intensity. In addition, the capability to solve missing data revealed crucial to improve the reliability of the proposed

system. Moreover, the preliminary results showed that the POMPES is lightweight for processing the self-report data obtained during the monitoring period.

These findings should be interpreted in light of several limitations. First, data imputation using linear regression is sensitive to outliers. Second, generalisability is should be addressed with caution due to the fact that our sample included a relatively homogenous group of patients (mostly Caucasian and middle aged) recruited from one treatment centre.

However, there is still room for improvement so that new studies should be addressed to compare several data imputation techniques so as to enhanced the performance of the proposed system. Moreover further work is needed to evaluate the proposed system to follow up participants for longer periods of time which includes a complementary study encompassing patients with chronic pain symptoms. At last, further studies are needed to evaluate the proposed system with parametric data.

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Chapter 8

Conclusions and Future Work

This chapter presents the main conclusions that result from the research work described in this thesis. Furthermore, it discusses a few research topics related with the work developed in the doctoral programme that may be addressed in the future.

1. Final Conclusions

This thesis is focused on IT for pain management and describes the research work developed with the purpose of presenting a new approach based on ubiquitous and interoperability information system. The research work aimed to be complementary and comprehensively so as to promote the improvement of research expertise regarding various topics such as: systematic review, meta-analysis, RCT, book chapter, paper on conference, and working paper. In addition, the research work was conducted following several standards and guidelines, namely: PRISMA statement, Cochrane Collaboration's tools, CONSORT statement and IMMPACT recommendations.

All assumptions resulting from the research work were tested in laboratory and/or in clinical setting so as to produce unequivocal and solid evidences of the proposed concepts and techniques. These assumptions were based on the critical review of mobile and web-based systems for pain management together with computer technologies used by CDSSs applied to pain. In addition a RCT was implemented so as to validate the proposed monitoring system model and the decision support model that sustains it was validated using Microsoft Excel and IBM SPSS Statistics. This research procedure resulted in contributions of this thesis leading to the accomplishment of the main objective of developing a monitoring system comprised with ubiquitous interfaces provided via mobile devices and Internet, using a safety and integrity data repository provided by a PHR and complemented for a decision support model that generates real-time alerts, and messages to HCP and patients.

The effective inclusion of HCP and patients together with interoperability and ubiquity capabilities raises concerns and challenges to the design, development and application of pain monitoring systems. The interaction with the system anywhere and at anytime offers opportunities to the healthcare delivery, promising to contribute to better treatments and outcomes based on monitoring

systems which aiming not only to produce accurate results but also to optimize human and material resources. Hence, several approaches have been proposed by researchers many of them are limited mainly due to the following topics. First, some computerised systems are designed to interact directly with patients without presence or supervision of HCP. Second, sharing and access to information by either HCP or patients, or both is often inexistent or unpractical. Third, these systems are mostly limited in terms of data integration with external systems and/or devices. Fourth, the reliability and accuracy of these systems are rarely proved. Fifth, the effects of computerised systems on HCP and patients outcomes remain understudied.

In line with this, the main goal of this thesis was to propose an alternative approach that does not suffer from the above-mentioned limitations. The secondary objectives were stated so as to divide the research work in theory and practice to accomplish the main objective. On the one hand, theory was based on the study of the existing solutions related to computer technologies used by CDSSs applied to pain management. This study presented the advantages and limitations of each solution in order to produce the state of the art, with special focus in the clustering of methods according the different machine learning techniques, and its description in terms of accuracy, symptoms, medical setting, main decisions, ubiquity, and accessibility. The literature review revealed the following machine learning techniques: rule based algorithms, artificial neural networks, rough and fuzzy sets, and statistical learning algorithms. In addition, terminologies, questionnaires and scores were content management techniques commonly used. Since these techniques involved too many variables it appears to be hard for medical experts to build valid models which may lead to low accuracy systems, resulting in inadequate or incorrect diagnosis. In addition, was observed the absence of assessment of the economic and social effects resulting from the use of these systems. Moreover, the excessive time required to complete the questionnaires and scores, the lack of integration with mobile devices, the limited use of web-based interfaces and the scarcity of systems that allow for data to be inserted by patients were all limitations that were detected.

On the other hand, theory was complemented by the study of the existing approaches related to mobile and web-based systems applied to chronic pain management. This study characterized the system in the following topics: reported key findings, objectives, patients conditions, participants, location (e.g. patient home, hospital, ...), data collected within the system, data complementary to the system, and the methodology used to transmit data between patient and HCP. Moreover, a defined list of 10 criteria was used to assess the quality of the systems. The literature review revealed the predominance of systems based on mobile devices (81%) over web-based systems (19%). Furthermore, the use of almost ninety different scales and questionnaires at pre, post or during

treatment were observed. The collected data comprised among others: location, duration and intensity of pain, consequences as the impact on quality of life, emotional and aversive aspects. This not only evidences the multi-dimensional condition of pain, but also represents challenges and concerns related to conception, development and implementation of computerised systems for pain management. This study also revealed that 44% of the systems transmitted data immediately after its acquisition, using Internet, personal computer or SMS. The remaining systems studies, 7% did not report the transmission method, whereas 49% collected data at intervals, in the clinic visit or at the end of the monitoring period. This study also presented a new model proposed to evaluate the effect of the computerised monitoring systems on different dimensions of pain. This model is based on a qualitative analysis stemming from the data fusion method combined with a quantitative model based on the comparison of the standard deviation together with the values of mathematical expectations. This methodology determines the effect resulted from the use of technology compared with pen-and-paper approach and was applied to several dimensions of pain. It was observed that pen-and-paper and technology produced equivalent effects in anxiety, depression, interference and pain intensity. On the contrary, technology evidenced favourable effects in terms of catastrophizing and disability.

The practice was based on the evaluation of the proposed system, including a RCT with ambulatory post-operative patients and simulations in laboratory so as to determine mathematical models to clinical decision support. The RCT was conducted at the Hospital Sousa Martins and included 32 participants between 18 and 75 years old, with acute pain resulting from surgical intervention. These participants were recruited over a six weeks period through speciality care physician referral from the ambulatory surgery department and were divided into treatment group that uses the proposed ED and control group. The study evidenced not only that the majority of participants recommend the system, but also that they recognized it suitability for pain management without the requirement of advanced skills or experienced users. Furthermore, the system enabled the definition and management of patient-oriented treatments with reduced therapist time. The guidance of HCP at the beginning of the monitoring is crucial to patients' satisfaction and experience stemming from the usage of the system as evidenced by the high correlation between the recommendation of the application, and it suitability to improve pain management and to provide medical information. There were no significant group differences regarding to improvements in the quality of pain treatment.

Based on the data collected during the RCT, a CDSS was developed so as to complement the proposed monitoring system offering capabilities of tailored alarms, reports, and clinical guidance. The

system, called Patient Oriented Method of Pain Evaluation System (POMPES), is composed for the following components: input, data imputation, analysis of variance, analysis of discrepancy and output. The input is adjusted in accordance with the treatment protocol and duration of the monitoring which may express different granularities from a single day to entirely week of self-reporting data. The data imputation aiming to replace missing values using an estimator based on a linear regression model. Whenever the data represents a normal distribution (Gaussian) the analysis of variance is obtained using the one-way ANOVA. Otherwise is used the Kruskal-Wallis test. The discrepancy analysis is determined based on the Tukey-Kramer principles. Finally, the output includes the results obtained from the test of significance of all elements that encompass the input and the qualitative analysis resulting from the comparisons among the multiple treatment periods.

The combination of data imputation and statistical models conducted to a fully accuracy related to decisions suggested by the system compared with the medical diagnosis. Thus, the POMPES system revealed it suitability to acute pain monitoring as evidenced its ability to detect either stability (standard case) or change (exceptional case) in pain intensity.

The main objective of this thesis was accomplished by the presentation of the monitoring system. This system enables ubiquitous access to HCP and patients so as to they are able to interact with the system anywhere and at anytime, and WS were using to send and receive data. In addition, the collected data are stored in a PHR which offers integrity and security of the data as well as permanent on line accessibility to both patients and HCP. This system is complemented by a decision support system based on a mathematical model which provides real-time alerts and messages oriented to HCP and patients resulting from the analysis of the collected data together with the patients' definitions. Furthermore, the system enables the management of patient-oriented treatments with reduced therapist time, and provides to HCP a better perceived control over the monitoring.

2. Future Work

Future studies should be addressed so as to assess economic effects, the contribution to improve the patient's treatments adherence and the effectiveness of the therapeutics provided by the proposed monitoring system. In this sense, new RCTs should be implemented so as to complement the current findings.

The data imputation of the proposed CDSS may be further developed whereby new studies should be addressed to compare several data imputation techniques. Finally, further work is needed to evaluate this system to follow up participants for longer periods of time which includes a complementary RCT encompassing patients with chronic pain symptoms which may lead to the design of novel mathematical models.