

**DEVELOPING A PATIENT-CENTRED OUTCOME
MEASURE FOR PATIENTS SUFFERING WITH
PERNICIOUS ANAEMIA**

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Preface

'What every physician wants for every one of his patient old or young, is not just the absence of death but life with a vibrant quality that we associate with a vigorous youth. This is nothing less than a humanistic biology that is concerned, not with material mechanisms alone, but with the wholeness of human life, with the spiritual quality of life that is unique to man. Just what constitutes this quality of life for a particular patient and the therapeutic pathway to it often is extremely difficult to judge and must lie with the consciousness of the physician'

(Elkington, 1966, p.714).

Abstract

Background: Pernicious Anemia (PA) is a potentially serious medical condition with a complex symptom profile that is under researched in the scientific literature. There is little consensus regarding its diagnosis, and individual differences in symptom perception and treatment expectation and outcome suggest the centrality of psychological factors in managing this condition. Health-related quality of life (HRQoL) has been suggested as an important health indicator in clinical outcomes in terms of determining the impact of illness on daily functioning, and subsequently informing health interventions. Given the absence of objective markers of patients' experience, the current thesis describes the development of a patient-centred measure for the identification and management of health-related quality of life in patients diagnosed with pernicious anaemia (PA-HRQoL), informed by the findings of four exploratory studies. The findings of these studies are supported by empirical evidence and provide rich information that reflect the burden of PA on individuals' quality of life.

Methods study 1: Study 1 reflected an audit of patients' records, aimed to establish the parameters for the focus of the instrument development through investigating the progression of patients from diagnosis through treatment and management of this condition. Data was collected on all PA cases (N=257, 189 females, 68 males, age range 25-97 years old, Mean age= 65, SD=17) in a pilot GP practice. Information recorded included demographics, symptoms, co-morbidities and treatment frequency.

Findings study 1: Results from this audit exercise indicated that specific tests carried out to diagnose PA (IFAB and GPC) were only requested for a small proportion of the sample. In some cases, discrepancies were noted regarding the outcome of these tests and an accurate PA diagnosis. Despite negative test results, some patients were diagnosed with PA, which may imply inconsistencies in the way PA is managed.

Patients presented with co-morbidities and symptoms such as extreme tiredness and shortness of breath as well with psychological symptoms such as feeling anxious and/or depressive. B₁₂ therapy was administered regularly (1-3 months) in most cases, as per WHO recommendation.

A few GP observations in the patients' records emphasized the experience of severe symptoms despite regular treatment. The findings of study 1 highlighted important clinical issues such as less routine testing than it would have been anticipated, having implications in terms of the quality of patient care.

Methods study 2: This was a qualitative study exploring individuals' perceptions of their PA experience. Specific questions regarding diagnosis and treatment (highlighted in study 1) were addressed in study 2, with a focus on individuals' perceptions of their PA experience. Semi-structured interviews were conducted with six females and one male whose ages ranged from 21 to 58 years, (SD=14) and analysed using thematic analysis.

Findings study 2: Themes revolved around the issues of misdiagnosis, illness perception and treatment effectiveness. Individuals' emphasized misdiagnosis and for some, having the illness affected their sense of identity, making it difficult to cope with daily living. Individuals' reported feeling better since undergoing treatment, however some felt the need for more frequent treatment, which in some cases was refused by their GP. Mixed feelings towards the support provided by health care services were expressed. Results of this study indicated that individuals' perceptions of PA are challenged when the legitimacy of their illness is questioned, increasing the psychological distress in these individuals and having detrimental effects on their health-related quality of life.

Methods study 3: A survey was carried out to investigate the PA experiences of members of the Pernicious Anaemia Society and to further explore the meaningful psychological variables that emerged from study 2. An online survey explored treatment supplementation, coping, illness identity, the impact of PA on one's quality of life and the provision of support, through the perspective of the members of the PA society (N=199, 172 females, 26 males; age range, 19 to 83 years old; Mean age = 45.5 years old, SD=13), by using a mix-methods approach.

Findings study 3: This study highlighted the frequent psychologizing of patients' symptoms (by clinicians), the inability to control and manage symptoms, suboptimal treatment, worry concerning prognosis and the poor provision of healthcare. Findings from this study have significant implications for the management of PA and highlight the importance of measuring psychological variables, which will serve as basis for the development of a patient-centred tool for the identification and management of health-related quality of life in this population.

Methods study 4: This study investigated illness severity and health-related quality of life in patients diagnosed with Pernicious Anaemia and involved the administration of psychological measures in patients recruited from two local GP practices as well as an online sample (N=184; 144 females, 40 males; Mean age = 56, SD=16). This study aimed to identify the best predictors of HRQoL, and to develop the HRQoL instrument. Multiple regression analyses indicated that physical HRQoL was best predicted by illness consequences and depression. Psychological HRQoL was best explained by the variables of illness identity, illness consequences, treatment control and depression. The HRQoL dimension of social relationships was best explained by depression. Environmental HRQoL was best explained by anxiety, illness identity and illness consequences. Exploratory factor analysis and a comprehensive review of the PA literature produced a 43-item HRQoL instrument measured across seven dimensions (physical functioning; psychological health; illness management behaviours; illness controllability and support; maladaptive coping; illness understanding and adjustment; distraction) with acceptable levels of internal reliability. These findings suggest that identifying patient needs may predict improvements in HRQoL.

Conclusions: The PA-HRQoL is the first attempt to identify and manage the HRQoL of patients with PA, contributing to the growing body of knowledge in this area. There is a crucial need for healthcare education in the recognition of PA symptoms, how symptoms impact on health-related quality of life and how these can be controlled. Validation of this instrument is yet to be established in further studies. It is anticipated that the PA-HRQoL may provide clinicians with accurate indicators of individual patient needs, therefore supplementing existing approaches to the PA management.

In future research, the PA-HRQoL may inform the development of interventions aimed at improving patient agency among PA sufferers. Further economic benefits could potentially include the reduction in both the frequency and length of consultations as a consequence of the diagnostic tool and the improved patient adjustment.

Keywords: pernicious anaemia, health-related quality of life, outcome, treatment control.

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List of abbreviations

BNF	British national formulary
BPS	British psychological society
BSCH	British committee for standards in haematology
CDC	Centers for disease control and prevention
DH	Department of health
FDA	Food and drug administration
GPC	Gastric parietal cell
HRQoL	Health- related quality of life
IFAB	Intrinsic factor antibody
NICE	National institute for health and care excellence
PA	Pernicious anaemia
PA-HRQoL	Pernicious Anaemia health-related quality of life questionnaire
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QoL	Quality of life
WHO	World health organisation

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Chapter 1

Introduction

Pernicious Anaemia (PA), also known as autoimmune metaplastic atrophic gastritis is an under-researched medical condition that leads to the destruction of the parietal cells in the gastric mucosa and reduced levels of stomach acidity. PA results from the failure to produce intrinsic factor (IF), a glycoprotein which is essential for the absorption of B₁₂ in the small intestine (Carmel, 2008). The clinical manifestations of PA vary according to the severity of the condition and may cause serious gastric, intestinal and psychiatric abnormalities. Common psychiatric symptoms include delusions (Bar-Shai, Gott & Marmor, 2011; Blundo, Marin & Ricci, 2011), depression (Milanlioglu, 2011; Hanna, Lachover & Rajarethinam, 2009; Durand, Brazo & Dollfus, 2003), irrational behaviour (Slade, Bharadwaj, 2010; Gomez-Bernal & Bernal-Perez, 2007) and social withdrawal (Sahoo, Avasthi & Singh, 2011; Rajkumar & Jebaraj, 2008). PA may also reflect varying degrees of neuropathy, causing irritation and lack of sensation in the hands and feet as well as mental changes including confusion and irritability (Springhouse, 2005; Sethi, Robilotti & Sadan, 2004).

Currently, the B₁₂ assay is unreliable where the result is borderline. According to current guidelines from the British Committee for Standards in Haematology (BCSH), patients diagnosed with PA require lifelong therapy with intramuscular vitamin B₁₂, every 3 months (Devalia, Hamilton & Molloy, 2014; NICE, 2014).

However, the response to B₁₂ therapy may vary markedly between patients and significant numbers request more frequent treatment to alleviate perceived symptoms.

In most cases, this is refused since clinicians perceive that symptoms presented by patients may be of a psychosomatic nature (Banka, Ryan & Thomson, 2011; PAS, 2008). The lack of flexibility to comply with requests for more frequent B₁₂ therapy may lead to increased patient anxiety and as a result, many patients purchase over-the-counter treatment in which safety is not guaranteed, to maintain what they perceive as being an acceptable quality of life (Hooper, 2012; Deale & Wessely, 2001). Patients often express dissatisfaction with the current standard of care, which reflects the 'one size fits all' regimen. This represents a dilemma for health professionals who are concerned with early medicalisation in mild and transient cases when there is no demonstrated clinical benefit of more frequent B₁₂ therapy (Devalia, 2006).

This thesis originated from the need to investigate the reason why some patients still experience severe symptoms, despite receiving frequent B₁₂ therapy. There is no instrument to assess the severity of patients' symptoms in this population. Also, it is currently unexplained whether any potential improvements in symptoms relate to patients' expectations towards treatment or if patients are in actual need of additional B₁₂ therapy. With this in mind, it proves difficult to determine the amount of treatment necessary for adequate patient response. The experience of ongoing symptoms and variability in treatment response may result from different factors such as time since diagnosis, the way individuals perceive their condition, the way they cope and/or the potential tendency to somatise symptoms.

In the absence of physiological parameters of patients' experience, it is crucial to assess how individuals make sense of their overall illness experience.

Therefore, assessing illness beliefs may be useful for clinicians to further understand the perceived severity of patients' symptoms, enabling them to select treatment strategies tailored to patients' needs (Nielsen and Jensen, 2004). Investigating illness severity based on beliefs about one's illness will serve as basis for the development of a patient-centred measure for the identification and management of health-related quality of life in patients suffering with Pernicious Anaemia. The development of the PA-HRQoL questionnaire, built from a patient's perspective, is the contribution to knowledge in the present thesis. To the researchers' knowledge, there is no reference to such measure in the current literature. This instrument derived from items included in well-established validated psychological measures (illness perceptions, health status, somatic focus, coping and HRQoL), as well as pilot work conducted throughout this thesis (Study 1- Study 4).

This instrument taps into seven areas that aim to identify HRQoL in this population. These include physical functioning, illness management behaviours, illness understanding and adjustment, illness controllability and support, maladaptive coping and distraction. Overall, the PA-HRQoL comprises of 43 items measured in a 5- point Likert scale. Once tested and validated, it may potentially be used in clinical settings to assess the severity of patients' symptoms .This will provide clinicians with a further understanding of how PA is affecting their patients.

This tool has the potential to adjust treatment according to individual needs, potentially leading to a more effective management and patient care, thus improving patients' health-related quality of life and reducing the care burden at primary and secondary levels.

Further economic benefits could potentially accrue to GP'S and NHS medical practitioners in terms of reduction in both the frequency and length of consultations. This instrument may also highlight patients in need of direct referral to other services to facilitate prompt and effective treatment.

Chapter 2

2.1 Literature review

The symptoms suffered as a result of PA are varied and non-specific. The response to B₁₂ therapy may vary markedly with some patients perceiving the need for more frequent replacement therapy than others. PA treatment is intended to limit symptoms, increase functioning and delay progression of the condition. However, the current standard of care may not reflect this, causing lifestyle restrictions that may impact on individual's quality of life. It is anticipated that the development of a patient-centred outcome measure for the identification and management of HRQoL, in a new area of clinical research, may potentially lead to a more effective approach to patient engagement and satisfaction with treatment.

This chapter will discuss the theoretical foundations that inform the current thesis. It will explain why applying a health psychology perspective (biopsychosocial approach) to the management of PA may prove valuable to both PA sufferers and health professionals. Based on this holistic view of patients' experience, this review will address the importance of investigating how patients' beliefs about their illness (illness representations) may significantly impact on how individuals adjust to their condition. Existing PA literature is mostly medical in nature and there is a gap in research tackling the psychological impact of PA. Given the dearth of research in this area, this section will present and discuss studies that reflect the impact of chronic illness on HRQoL. It will also discuss the need to include patient-reported outcomes when measuring HRQoL, as indicators of increased clinical functioning. It will then discuss the implications of early screening in PA.

2.1.1 A health psychology perspective on Pernicious Anaemia

The World Health Organisation has defined health as the ' complete state of physical, emotional and social well-being and not merely the absence of infirmity or disease' (WHO, 1948). Health psychology focuses on the concept of health as a continuum by exploring how psychological factors may impact on health by considering illness onset and progression, the direct and indirect pathways between psychology and health and variability.

The definition of Health psychology represents the “aggregate of the specific educational, scientific and professional contribution of the discipline of psychology to the promotion and maintenance of health, the promotion and treatment of illness and related dysfunction” (Matarazzo, 1980, pg.815). Health psychology claims that illness can be caused by a combination of biological, psychological and social factors and is therefore rooted on a biopsychosocial framework (Ogden, 2012). The biopsychosocial paradigm (Engel, 1977, 1980) emerged from the need for a more contextual and inter-disciplinary approach in relation to the reductionism reflected by the biomedical model, a disease oriented approach, which has been very useful in the treatment and control of infectious diseases. However, with the increased prevalence of chronic conditions, its efficacy is limited since it neglects the patient and their experience (Borrel-Carrió, Suchman & Epstein, 2004). The biomedical model implies a linear relationship between pathophysiology and progression of illness; however, this relationship has been challenged by evidence suggesting that psychosocial and environmental factors play an important role in this process by either aggravating illness or leading to positive outcomes (Tanaka, Kanazawa, Fukudo & Drossman, 2011; Pakenham, 2005).

The biopsychosocial model has served as basis for the development of research investigating how psychological and social factors may influence the course, development and outcome of a condition. This approach has led to developments in the field of health psychology as well as psychoneuroimmunology. The biopsychosocial model reflects a holistic approach to patient care by looking at the biological aspects of the person (e.g. organs and tissue), psychological (such as attributes and habitual factors) and the social facet (including the physical and social environment interacting with the individual). Thus, the biological aspects refer to the physiological causes of disease, including genetic issues, hormones, immune function, stress reactivity, neurochemistry and physical trauma. However, physiological causes alone do not always adequately explain the occurrence of illness. The psychological factors in this framework relate to cognitive, emotional and behavioural aspects that may directly or indirectly influence an individual's health. In this way, attitudes, beliefs, emotions, negative life events, coping, social skills and behaviour play a significant role in one's condition. The acknowledgment that psychological factors play an important role in the aetiology and course of a condition has been substantiated in the literature (Knowles et al., 2014; Khayyam-Nekouei et al., 2013; Nash, 2013). A review looking at the psychological adjustment in chronic illness has suggested that a sense of control and mastery are important indicators of illness adjustment (Ridder, 2008). Evidence of the protective role of optimism on health status has also been linked with active coping and reduced incidence of anxious and depressive symptoms in cancer patients (Gustavsson-Lilius et al., 2012; O'Brien & Moorey, 2010) and with decreased incidence of coronary heart disease (Tindle et al., 2009).

The social factors are relevant to the individual and his/her environment by determining external factors that play a role in the manifestation of illness, including social relationships, the physical environment, culture, social support and access to health care (Engel, 1977, 1980). The diagram below outlines the systematic relationship between these factors, put forward by Engel (1980) (Fig.2.1.1).

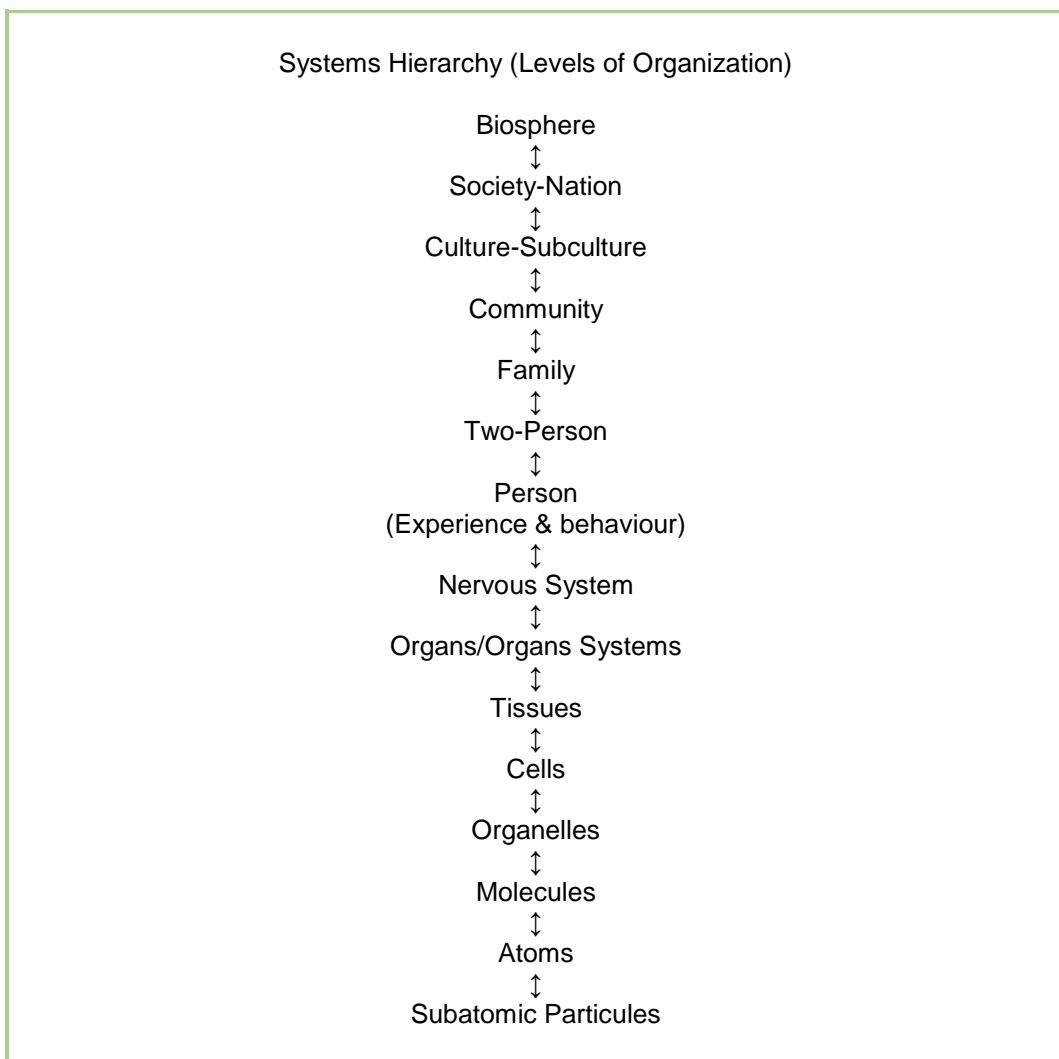


Figure 2.1.1 The Biopsychosocial model, Hierarchy of Natural Systems. Engel.G.L (1980). The clinical application of the biopsychosocial model. Am J Psychiatry, 137(5).

The hierarchy of natural systems reflects the interaction of levels where every level is a component of a higher-system being regarded at the same time as a whole and as a part. According to Engel, this represents a way of understanding how disease and illness are affected by multiple levels of organization, from the molecular to the societal (Engel, 1980). Applying the biopsychosocial model to the understanding of PA pathophysiology suggests that psychosocial factors and their interaction with physiological mechanisms involved in the process of vitamin B₁₂ absorption in the gut, may change symptom severity, influence illness experience, and affect health-related quality of life.

Currently, there is no research addressing the variables contributing to HRQoL in PA and the variability in treatment response is currently unexplained. The application of a biopsychosocial framework within a health psychology perspective would be useful for clinicians to understand patient's perceptions that may influence health behaviour and therefore the patients' condition.

2.1.2 Illness representations

PA has the potential to cause serious complications for its sufferers, however the extent of psychosocial difficulties likely to be experienced by patients is unknown and the processes that may render an individual vulnerable to such difficulties are not fully understood. Previous research has stressed the crucial role that subjective beliefs play in the way individuals' make sense and cope with their existing condition, as significant predictors of illness adjustment (Leventhal, Meyer & Nerenz, 1980).

The common Sense Model of Self-regulation forms a theoretical basis to assess individual's perceptions of a health threat. Self-regulation represents a dynamic motivational system in which the management of emotional responses in relation to the experience of illness are linked to cognitive processes.

This model suggests that illness perceptions influence coping strategies and coping mediates the relationship between illness perceptions and health outcomes (Leventhal, Meyer & Nerenz, 1980). This model has been conceptualised in three stages, identification, coping strategies and appraisal. Identification reflects illness representations and emotional responses. Coping strategies are then generated in response to illness representations. The last stage reflects the appraisal of coping strategies (see fig.2.1.2).

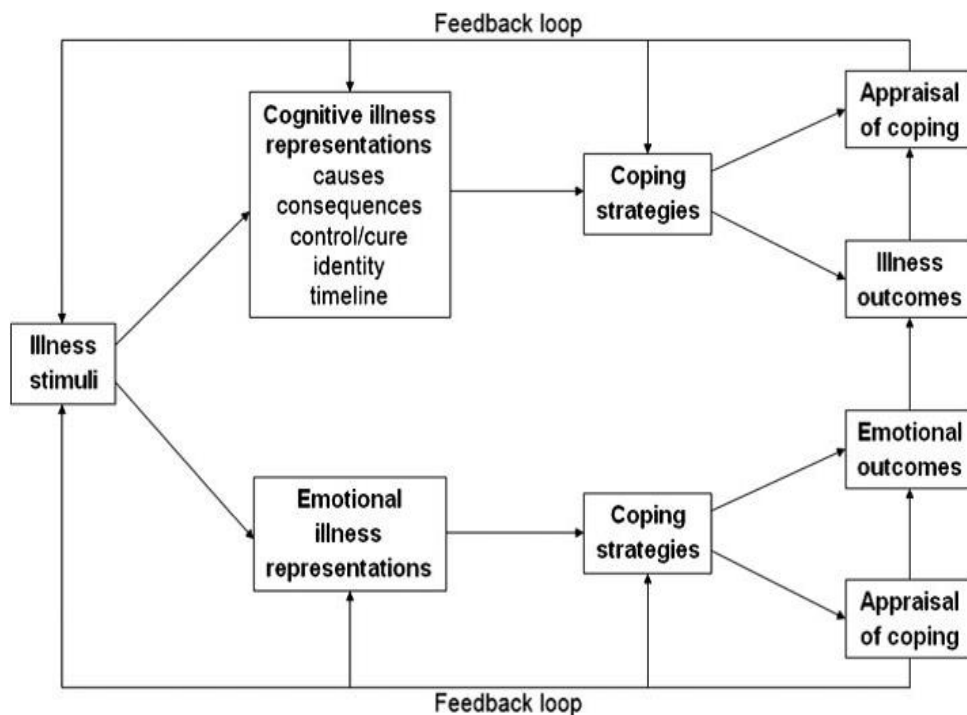


Fig.2.1.2 The common sense model of illness danger. Leventhal, H., Meyer, D., & Nerenz, D. (1980). In S. Rachman (Ed.), Contributions to Medical Psychology (Vol. 2, pp. 7–30. New York: Pergamon Press.

This model is structured according to five cognitive dimensions, identity, timeline, consequences, cause and cure/ controllability, having a significant impact on illness outcome (Leventhal, Nerenz & Steele, 1984; Leventhal, Meyer & Nerenz, 1980).

Identity consists of how individuals label their illness and perceived associated symptoms. The cause reflects beliefs about factors contributing to the illness onset. The timeline refers to beliefs concerning the onset and the expected duration of the illness (e.g. acute, cyclical or chronic). The consequences relate to the perceived effects of the illness on physical, social, economic and psychological well-being, including beliefs about the severity of the same. Lastly, cure and control refers to the extent to which one can control the health threat. According to Leventhal and colleagues (1997), illness representations are organised into clusters. In this way, a strong belief that the illness can be controlled or cured is likely to be linked to the belief that the illness will last a short time, having relatively minor consequences. Alternatively, a strong belief that the illness will last a long time is likely to be associated with an illness that can't be cured or controlled and with a belief in more serious illness consequences (Leventhal et al., 1997).

The common sense model of self-regulation has been used to investigate the relationship between illness representations, illness response and outcomes in various conditions such as diabetes and multiple sclerosis (Hagger & Orbell, 2003; Jopson & Moss-Morris, 2003).

Previous research has reported the inter-relationship between these dimensions. A strong illness identity has been associated with perceptions of high chronicity and perceived low illness control, resulting in serious consequences for individuals such as impaired health-related quality of life (Larun & Malterud, 2007; Vaughan, Morrison & Miller 2003; Heijmans, 1998; Moss-Morris, 1998; Scharloo et al., 1998; Weinman, Petrie, Moss-Morris & Horne, 1996).

Studies have found impaired HRQoL in a variety of chronic conditions, to be associated with higher symptom frequency and severity, distress, functional impairment, poor psychological well-being and mood disturbances (Chen & Chen, 2016; Megari, 2013; Franzén, Saveman & Blomqvist, 2007; Lett et al., 2004; Lam and Louder, 1999). Alternatively, increased HRQoL has been associated with the experience of fewer symptoms, better disease understanding, better treatment control and less emotional response (Weldam et al., 2014; Covic et al., 2004).

Leventhal's model of illness representations addresses the importance of assessing peoples' cognitive representations of illness to achieve better illness outcomes. There is a lack of empirical evidence concerning the nature of psychological factors implicated in PA, mainly regarding individual differences in symptom perception and treatment expectation, and how these factors may impact one's health-related quality of life. By investigating the role of illness perceptions and related variables such as coping strategies and health status will prove valuable in understanding how these variables may be associated with PA adjustment.

2.1.3 Quality of life and health-related quality of life

Quality of life (QoL) is a subjective and complex construct that refers to individuals' perceptions of their position in life, which is related to their goals and expectations, being also determined by their culture and value systems. A person's physical health, independence, psychological state, belief system, spirituality, religion and social and environmental relationships have all been proposed to influence one's quality of life (WHOQOL Group, 1998, p.1569).

The term health-related quality of life (HRQoL) covers aspects that are relevant to one's health. Therefore, there is no established definition of HRQoL as interpretations may vary from a holistic focus on the social, emotional, physical well-being and functioning to descriptions of the impact on an individual's health and his/her ability to lead an accomplished life (Fayers & Machin, 2000). HRQoL also includes both subjective and objective components that are necessary to the construct. The former focuses on how the individual perceives or appraises their health status in terms of emotions, life satisfaction and well-being. The objective component is related to the individual's ability to function according to their degree of health, which, may include self-care, and the experience of symptoms such as tiredness and pain. Therefore, subjective perceptions transform objective functioning in the HRQoL experienced by the individual. In this way, individuals' scores on objective and subjective rated measures of quality of life vary markedly (Megari, 2013; Eiser, 2004, as cited by Lin et al., 2013; Fakhoury & Priebe, 2002; Testa & Simonson, 1996).

The following table highlights discussions of definitions linked to quality of life in the literature.

Table 2.1.3.1

Examples of definitions of quality of life and health-related quality of life in the literature

- a) 'Quality of life refers to patients' appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be ideal.' (Cella & Tulskey, 1990)
 - b) 'Quality of life is an individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.'(WHOQOL Group, 1993)
 - c) 'Quality of life measures the difference, or the gap, a particular period of time, between the hope and expectations of the individual and that individual's experiences.' (Calman, 1984)
 - d) 'Health-related quality of life is the value assigned to duration of life as modified by the impairment, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy.' (Patrick & Erikson, 1993)
 - e) 'Health-related quality of life refers to the level of well-being and satisfaction associated with an individual's life and how this is affected by disease, accidents and treatments from the patient's point of view.' (Lovatt, 1992)
-

In the patient's perspective, the impact of illness is associated with the perceived ability to carry on with daily life (Hale, Theharne & Kitas, 2007; Chrischilles, Rubenstein, Voelker, Wallace & Rodnitzky, 2002). The increased prevalence of chronic illness over the years has been associated with a great impairment in HRQoL, significantly impacting on healthcare delivery (Megari, 2013; WHOQOL Group, 1998). The clinical features of chronic conditions and the need for lifelong treatment pose a significant threat to individuals' health status.

For chronic illness patients, maintaining a good quality of life is essential for disease management and psychosocial adjustment (Davison & Jhangri, 2013; McGee, 2001).

2.1.4 Health-related quality of life measurement

Measures of health-related quality of life share two common assumptions. Firstly, these are multidimensional in their appraisal of health and secondly focus on the subjective individual evaluations rather than the perceptions of the healthcare professionals or significant others (Bennett et al., 2002). There has been a growing interest in both generic and disease-specific evaluations of health-related quality of life (Bowling, 2001).

Generic measurements allow for comparisons between and across conditions in relation to dimensions of overall health status and functioning, with the potential to generate unexpected findings. Generic tools include health profiles and utility measures such as the quality-adjusted life-years (QALY's; Guyatt, Feeny & Patrick, 1993). QALY's are calculated by multiplying the years of life by morbidity score on a quality of life scale where zero will reflect death and one will reflect full health. Morbidity rates, survival periods, clinical assessments, laboratory tests and social measures (e.g. hospital remission rates) constitute examples of traditional utility measures. However, one of the issues of using QALY's relates to the notion that people suffering from severe illness may not rate their quality of life as significantly poorer than people with mild illness may, or healthy people, therefore comparisons between different groups of patients may be difficult (Higginson & Carr, 2001). Utility measures of quality of life reflect on the evaluation of certain aspects of health such as mobility and symptoms by professional or laypeople, which may not account for the individual perspective.

However, these measures only seldom cover the emotional and psychological consequences of disease (Aaronson, 1988). While generic questionnaires are typically used to assess HRQoL in different populations, condition-specific instruments are developed to target specific aspects of health that are relevant to a particular patient group, potentially ensuring greater clinical validity and responsiveness to changes that are meaningful to patients (Megari, 2013; Cella & Nowinski, 2002).

Condition-specific measurements possess the advantage of discriminating between patient's illness severity levels as well as being more sensitive to clinical outcomes. The criteria to evaluate outcome of care varies across different conditions and this is reflected in the condition-specific HRQoL scales. Examples of condition-specific measures include the Arthritis Impact Measurement Scales (AIMS; Meenan, 1980, 1991, 1992), assessing the physical, social and emotional well-being of individuals. The Inflammatory Bowel Disease Questionnaire (IBDQ; Guyatt et al., 1989), addresses domains such as gastrointestinal symptoms, systemic symptoms, emotional health and social function, and the MacNew Heart Disease Health-related Quality of Life Questionnaire (MacNew; Hillers et al., 1994) is designed to evaluate the physical, emotional and social function dimensions of coronary heart disease and its treatment.

As opposed to condition-specific measures, dimension-specific measures of health-related quality of life focus on certain aspects of health such as anxiety, depression and psychological well-being. Examples include the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock & Erbaugh, 1961) and the Psychological General Well-Being Index (PGWB; Dupuy, 1984).

The decision to use generic or condition specific tools is linked with the aims and expected outcomes of a particular study, as its content should reflect the nature of the condition under study as well as response to treatment (Bennet et al., 2002).

Authors suggest that using generic measures alongside disease measures ensures a wide coverage of health related dimensions. This is also useful when addressing clinical issues as well as detecting unexpected positive and negative intervention outcomes in clinical trials (Fitzpatrick et al., 1998, as cited by Bowling, 2001). In this way, an individual suffering with pernicious anaemia would be expected to undergo investigations for serum B₁₂ levels in the blood.

The lack of a clear foundation for quality of life assessments has resulted in the difficulty in choosing research appropriate tools (Moons, 2004). Nonetheless, available generic instruments have been proven suitable in terms of the initial assessment of the health-related quality of life of individuals suffering with various chronic conditions (Longworth et al., 2014; Skevington, Lofty & O'Connell, 2004). Currently, there is no available tool designed to obtain health-related quality of life information in patients with B₁₂ deficiency and/or pernicious anaemia and patient-centred measures that have found to be useful in other chronic conditions may be of little relevance for this effect (Hillers et al., 1994; Aaronson et al., 1993; Meenan, 1992; Guyatt et al., 1989). The development of patient-centred measures related to quality of life reflects the international focus in providing effective evidence-based health care (Bowling, 2001).

2.1.5 The application of generic health-related quality of life instruments in chronic illness

Whilst there is an array of measures effectively assessing health-related quality of life in different groups of individuals, some measures may be more pertinent to certain groups when compared to others. Therefore, the selection of appropriate HRQoL measures needs to consider essential criteria such as the concepts under measurement as well as the psychometric properties of the scales under development. HRQoL assessment is also important in terms of evaluating the impact of primary care services. Health-related quality of life measures have been widely applied in the area of chronic illness by covering domains that are relevant to chronic conditions such as physical functioning, pain and general health. The associated co-morbidity in chronic conditions such as diabetes, arthritis, chronic obstructive pulmonary disease and congestive heart failure is generally translated into poorer quality of life (Haroon et al., 2007; Alonso et al., 2004).

A comprehensive systematic review was conducted by Hand (2016) to identify generic profile-type HRQoL scales for adults with chronic conditions. The search criteria were limited to English publications and reviews in order to detect the most widely used scales. Inclusion criteria comprised generic scales that were developed for clinical use, short, easy to complete and score, and applicable to primary care patients with varying diagnoses. It also included scales that covered broad content areas (physical, psychological and social domains) and scales that included individualized items.

The search elicited nine scales, which included the Sickness Impact profile, the Health Assessment Questionnaire, the World Health Organization Quality of Life Scale (WHOQOL-100), the Dartmouth COOP Functional Assessment charts, the Duke Health Profile, the Nottingham Health Profile, the Short Form Health Survey (SF-12), the Short Form Health Survey (SF-36) and the WHOQOL-BREF. This review also acknowledged the three most suitable generic assessments for this effect, based on its theoretical basis, content development, psychometric properties, scoring and feasibility. The instruments included for review were the Short-Form Health Survey-36 the Duke Health Profile and the short version of the WHOQOL-100, the WHOQOL-BREF. Considering that the primary endpoint of this thesis is to develop a screening tool for pernicious anaemia, a good starting point would be to consider established health-related quality of life measures. Therefore, it seems practical to use Hand's review as a reference (please refer to table 2.1.5.1). The scales identified in the review can be found below.

The Short-Form-36 Health Survey (SF-36; Brazier et al., 1992; Ware & Sherbourne, 1992)

This survey comprises of 36 items developed from the Medical Outcomes Study Questionnaire with the objective of evaluating health status in clinical practice and research in chronic conditions as well as being applicable for use in healthy individuals. It provides a general indication of health status covering eight dimensions, physical functioning, role limitations resulting from physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations resulting from emotional problems and mental health. The SF-36 is also useful when used along disease-specific tools in clinical research.

Reliability and validity are acceptable in different patient groups with chronic or psychiatric conditions (Hubanks & Kuyken, 1993; Jenkinson et al., 1993; McHorney et al., 1993). However, a greater variance in scores have been reported (ceiling and floor effects), (McHorney et al., 1994).

This scale has also been found to be non-responsive to clinical change, possibly due to comorbidity issues (Spertus et al., 1994). Nevertheless, the SF-36 was found to be more sensitive to changes in health-related quality of life as compared to the Nottingham Health Profile as well as more precise than its shorter versions (SF-12; Ware et al., 1995; SF-8; Ware et al., 2001).

The Duke Health Profile (Parkerson & Broadhead, 1990)

This instrument was developed as a measure of adult functional health status in primary care settings. It was derived from the Duke-UNC Health Profile, comprised of 63 items across four dimensions reflecting the WHO definition of Health (symptom status, physical function, emotional function and social function). The shorter version, the Duke Health Profile, consists of 17 items across six dimensions (physical, mental, social, general health, perceived health and self-esteem). Five of the scales assess dysfunction in terms of anxiety, depression, pain and disability. Scores from the anxiety and depression subscales make up for the anxiety-depression scale. The elements in the Duke Health Profile may be scored separately, combined into an overall quality of life score or grouped into several measures. The Duke Health Profile reflects a self-administered or interview tool used in the clinical setting as a measure of medical, economic and social interventions on health and disease. Reliability studies suggest good internal reliability (Hubanks & Kuyken, 1993). However, floor and ceiling effects are apparent when compared with other measures such as the Nottingham Health Profile.

Furthermore, the physical health scale does not seem to perform well as it lacks specificity. In terms of the overall performance, the Duke Health Profile seems sound in terms of measuring overall health-related quality of life, being analogous to the SF-36.

The World Health Organization Quality of Life Assessment (WHOQOL-BREF; Skevington, Lofty, O'Connell & WHOQOL group, 2004)

The WHOQOL-BREF was originally developed from data from the field-trial version of the World Health Organization Quality of Life Scale (WHOQOL-100 Skevington, 1999; WHOQOL Group, 1994). The WHOQOL-BREF comprises two elements from the Overall Quality of Life and General Health and one item from each of the 24 dimensions present in the main version. The WHOQOL-100 was designed for determining the impact of health on an individual's life, taking into account the doctor-patient relationship. The WHOQOL-100 may also be used as a primary or secondary measure in clinical applications through monitoring progress after treatment or serving as an outcome measure. This tool may also be used in health surveys and epidemiological studies. It consists of 100 items covering six broad domains including physical and psychological health, level of independence, social relationships, environment, spirituality, religion and personal beliefs having the advantage of being applied across cultures enabling comparative results (Cazzorla et al.,2012;Orsel, Akdemir & Dağ ,2004;Skevington & Wright, 2001;O'Carroll et al, 2000; Power, Harper & Bullinger, 1999;Skevington, 1999; Bonomi et al.,2000). The psychometric properties are very good and the strengths of the WHOQOL-100 include its universality and focus on the patient (McDowell, 2006).

In abbreviated format, the WHOQOL-BREF is measured across four domains, physical health, psychological health, social relationships and environment and it has good to excellent psychometric properties of reliability and validity. It has been employed in different areas such as medical practice, research and audit, policy making as well as assessing the effectiveness of different treatments.

It may also be used to assess cross-cultural variation, to compare sub-groups within the same culture and to measure change across time in response to change in life circumstances (Baumann, Erpelding, Régat & Collin, 2010; Min et al., 2002). The WHOQOL tools reflect the views of individuals regarding their condition.

All of the measures described above address the physical, mental and social domains of health, in line with the definition put forward by the WHO (1948). The WHOQOL-BREF also assesses environmental aspects that may influence an individual's health status. Its development stems from a conceptual framework, which is stronger when compared with the other two scales. Information regarding the psychometric properties is less available for the duke health profile as well as the small amount of individualized items, which makes it less useful for patients with chronic conditions. The SF-36 has been reported as being useful when evaluating outcomes to improve health status. The WHOQOL-BREF does not have floor and ceiling effects and has the advantage of having the highest proportion of individualized elements, which makes it useful to apply in adults with chronic conditions and therefore PA sufferers.

Despite some caveats, such as the uncertain ability to detect meaningful change with patients suffering from chronic conditions, it seems that the WHOQOL-BREF may be one of the most suitable instruments to be used in adults with chronic conditions in primary settings. The areas covered are broad, outcomes may be assessed in clinical practice and it addresses individual's concerns. Given the nature of the present thesis, the WHOQOL-BREF seems as the most appropriate measure to use for patients with PA and its associated co-morbidity. This measure is an asset for research when compared with other health-related quality of life measures that may be too broad or less practical to use in health care settings (WHOQOL Group, 1998). Please refer to table 2.1.5.1.

Table 2.1.5.1

The psychometric properties of scales measuring health-related quality of life in individuals suffering with chronic conditions (e.g. cardiac conditions, arthritis, diabetes or chronic obstructive pulmonary disease).

HRQOL scales	The Duke Health Profile	SF-36	WHOQOL-BREF
Scale description	17 items	36 items	26 items
Domains	Physical, mental and social health; general and perceived health; self-esteem, anxiety, depression, pain and disability	Physical function, mental health, social function, physical role, emotional role, pain, vitality, general health	Physical, psychological, social and environmental
Individualized items	5 individualized items	16 individualized items	20 individualized items
Validity	Evidence of discriminant(Parkerson et al., 1990,1992) convergent(Parkerson et al., 1990,1991,1992) and predictive (Parkerson et al., 1995) validity among primary care patients	Conflicting evidence found regarding the factor structure(Kosinski et al., 1999;Wolinsky et al.,1998;McHorney et al.,1993; Evidence of discriminant(Ten Klooster et al.,2013;Linde et al.,2008; Parshall et al.,2008;Whitfield et al.,2006;Salaffi et al.,2005;Brown et al.,1999; Kosinski et al.,1999;Woodcock et al.,2001;Lalonde et al.,1999;Ruta et al.,1998;Wolinsky et al.,1998;Prieto et al.,1997; McHorney et al.,1993) convergent(Ten Klooster et al.,2013;Cruz et al.,2009; Linde et al.,2008; Kosinski et al.,1999;Stavem et al.,1999; Ruta et al.,1998;and predictive validity (McHorney, 1996)	Evidence of factor structure of the scale(Skevington et al.,2004;Taylor et al.,2004;WHO,1998) discriminant(Liang et al.,2008;Norekval et al.,2007; Skevington et al.,2004; WHO,1998) and convergent validity (Cruz et al.,2009;Haroon et al.,2007; Taylor et al.,2004)

HRQOL scales	The Duke Health Profile	SF-36	WHOQOL-BREF
Reliability (Cronbach's alpha)	Good levels of reliability in primary care patients ($\alpha=.85$) for the emotional subscale, (Parkerson et al., 1995). Lower levels of reliability in certain subscales ($\alpha=.55-.78$), (Parkerson et al., 1990, 1992)	Evidence of good levels of reliability ($\alpha=.75-.95$) in all subscales in some studies (Ten Klooster et al., 2013; ;Linde et al., 2008 Kosinski et al., 1999;) however lower reliability found for the social function scale ($\alpha>.60$) (Ruta et al., 1998; Prieto et al., 1997).	Good levels of reliability for 3 subscales ($\alpha=0.80-0.87$) and lower levels for the domain of social relationships ($\alpha=.64$) (Taylor et al., 2004; WHO, 1998).
Responsiveness	Evidence of responsiveness in most subscales for individuals undergoing cardiac rehabilitation (Parkerson, 2002)	Evidence of responsiveness found for most subscales generally for adults with chronic conditions.	Evidence of responsiveness found for the physical and social domains in adults suffering from rheumatoid arthritis (Taylor et al., 2004)
Scoring	Each question has 3 possible answers, rated 0, 1 or 2. Responses to the items in each measure are added together and then the means of the raw item scores are normalized to a scale of 0 (worst) to 100 (best). Responses are presented in the form of a profile of the scores calculated for each of the domains.	Precoded numeric values are recoded and then each item is scored on a 0 (low) to 100 (high) range. Then items in the same scale are averaged together to create each scale. Scale item scores represent the average for all items in the scale answered by the participant.	This scale derives four domain scores. Two items are derived in separate (overall quality of life and overall perception of health). The mean score of items within each domain calculates the domain score.
Acceptability and appropriateness	Issues with measurement noted. It may be self-administered or through interview.	Self-administered, postal or interview administered. Coverage of a wide range of areas affected by ill health. However, it has been suggested to fail to address certain areas related to function such as sleep.	Acceptability and feasibility in a wide range of conditions. A high quality patient-centred generic tool suitable for individual assessment, research and audit.

Adapted from Hand (2016). Measuring health-related quality of life in adults with chronic conditions in primary care settings. Canadian Family Physician, 62: e375-e383.

2.1.6 Health-related quality of life and its impact on chronic illness

The studies that will be reviewed below reflect the broad investigation of HRQoL and are helpful in terms of providing an insight into how chronic illness may influence different areas of an individual's life. Research has documented poor levels of HRQoL in individuals experiencing a variety of chronic conditions. In some studies, impaired HRQoL has resulted from low feelings of personal control and limited functional ability (George, Bergin, Clarke, Courtney & Codd, 2016; Riihimäki et al., 2016; Megari, 2013). In other studies, increased HRQoL has also been linked to illness acceptance, positive affect and social support in different chronic conditions (Vilhena et al., 2014; Eaton, Bradley & Morrissey, 2014; Kurpas et al., 2013). Self-management in chronic disease has been pointed out as an important factor related to improved HRQoL (Benzo, Abascal-Bolado & Dulohery, 2016; Pouver & Hermanns, 2009). The findings of these studies need to be examined by considering factors such as the type of condition under study as well as levels of co-morbidity (Muldoon, Barger, Flory & Manuck, 1998). The relationship between HRQoL, co-existing conditions and acute health care use was explored in a prospective longitudinal cohort study with 1999 adult participants (mean age of 63 years old) suffering from various chronic conditions such as diabetes, chronic respiratory disease and cardiac disease. Participants were enrolled in a chronic disease management program and HRQoL was measured through a self-report utility assessment covering five dimensions (independent living, social relationships, physical senses and psychological well-being). Findings suggested that the number of comorbidities and levels of HRQoL predicted acute health care use over three years of follow-up, and that poor HRQoL was predicted by an increased number of co-morbidities.

However, the authors noted concerns such as sample bias, as the participants of the study were enrolled in disease management programs; and the possible underreporting of co-morbidities as these were assessed through previously recorded administrative data (Hutchinson et al., 2015).

HRQoL has also been investigated in 535 patients suffering from chronic kidney disease in different stages of the condition at the start of dialysis treatment. Assessment was made in conjunction with clinical markers such as blood and hormone analyses. HRQoL was measured using the Short-Form health survey (SF-36) and was found to be significantly impaired across all domains that include physical function, social function and role limitations caused by emotional problems.

Poor physical functioning and impaired general health were prominent in the later stages of the condition. Patients in earlier stages of the condition also reported deteriorated HRQoL compared to matched controls. Co-morbidity was also found to be an important predictor of reduced HRQoL along with disease biomarkers such as reduced renal function (Pagels, Söderkvist, Medin, Hylander & Heiwe, 2012).

A multicentre study examining the response to replacement therapy for patients suffering from primary hypothyroidism has reported low levels of HRQoL in untreated patients particularly in the physical and emotional facets, regardless of biochemical status (Vigario et al., 2013). Another study assessing HRQoL in thyroid disorders has found greater impairment in domains such as physical and emotional role, general health and social functioning, in the absence of physiological measures. Mood and behaviour disturbances have been reported to influence poor health-related quality of life (Bianchi et al., 2004).

A retrospective cross-sectional study investigated the relationship between anaemia and HRQoL and activities of daily living in 838 long-term care residents. Data was achieved through a patient database. The findings of this study suggested that declines in haemoglobin levels in anaemic residents led to poorer levels of HRQoL and reduced physical functioning, independent of demographic characteristics (Bailey, Reardon, Wasserman, McKenzie & Hord, 2012). A few methodological issues were noted, such as the measurement of HRQoL which was largely assessed by proxy (e.g. spouse or healthcare professional), limiting the quality of the data.

Also, the measurement of anaemia status was performed by using a single haemoglobin index value, making it difficult to accurately determine whether individuals were suffering from acute or chronic anaemia.

2.1.7 Measuring HRQoL in patients suffering from chronic illness: the inclusion of patient reported outcomes

Existing research has emphasized the beneficial role of patient reported outcomes (PROs) in clinical health research (Nelson et al., 2015; Deshpande, Rajan, Sudeepthi & Nazir, 2011). A patient reported outcome (PRO) may be defined as any patient account of their health status, as opposed to an observer reported outcome (FDA, 2011). Patient reported outcome measures (PROMs) are designed to evaluate HRQoL and the quality of care delivered to patients by focusing on the patient perspective. PROMs are developed to improve the doctor-patient relationship by bridging the gap between both health professional and patient's concerns and therefore tailoring treatment to individual needs, (Barry & Edgman-Levitan, 2012) substantially improving patient satisfaction with care (Chen, Ou & Hollis, 2013; Marshall, Haywood and Fitzpatrick, 2006). Even though the use of PROMs has been suggested as valuable, their use may have also been limited (Snyder, Jensen, Segal & Wu, 2013; Haywood, Marshall & Fitzpatrick, 2006). Barriers to using PROMs may be linked to factors such as worry about emotional involvement with the patient, a professional identity based on the biomedical stance or lack of awareness of the impact of psychosocial factors in the progression of illness (Zimmerman & Tansella, 1996). The issue of patient burden and focus on elements that may bear more value to the health professional have also been put forward as reasons that may restrict the use of PROMs (Nelson et al., 2015; Manary, Boulding, Staelin & Glickman, 2013).

Research documenting the advantages of using PROMs, has been useful in tracking the benefits of consistent treatment over time. For example, the routine use of PROMs in clinical visits has resulted in lower disease activity in patients with rheumatoid arthritis (Hendrikx, de Jonge, Fransen, Kievit & van Riel, 2015) and it has led patients to report improved health in conditions such as depression (Ahles et al., 2006). The use of PROMs has been varied, from investigating the health outcome of surgery patients to using Web-based applications to the monitoring of health-related quality of life of patients suffering from serious conditions (Devlin & Appleby, 2010; Devlin, Parkin & Browne, 2010; Haverman, Engelen, van Rossum, Heymans & Grootenhuis, 2011). In conditions such as cancer, PRO tools are used to assess HRQoL to identify the needs of supportive care, the negative impact of treatment when survival time is long as well as identifying problems to enable clear communication in clinical practice (Acquadro et al., 2003). PROMs are best achieved if they are co-developed with patients and health professionals. Patients often report the need for better outcomes, reflected by the development of better systems of care (Devlin & Appleby, 2010). The development of a disease-specific measure, based on patient reported outcomes, relates to the primary endpoint of the current thesis.

The investigation of distinctive indicators of illness burden (e.g. symptom severity) may potentially fuel decision making in terms of how PA is managed, resulting in more effective treatment practices. This may improve patients' satisfaction with treatment and improve the patient and clinician rapport. Since clinical indicators of disease do not provide enough information to improve the quality of services provided to patients, the use of HRQoL tools based on a patient perspective may serve as guidance to improvement of these services (Chen, Lu & Kochen, 2005).

2.1.8 The cost-effectiveness of early screening in the management of Pernicious Anaemia

Traditional methods of assessing change in patients have been focused in laboratory and clinical tests. These methods often provide a clinical picture of the patient in terms of disease progression; however, these methods do not take into account the personal and social context that may influence the course of a condition (Higginson & Carr, 2001). Even though quality of life assessments have been widely used as an aid to measure adjustment and evaluate treatment, there is a concern that in general, these measures are not routinely used in clinical practice (King et al., 2016; Baumstarck et al., 2013).

The practicality of using these measures carries a great value in terms of facilitating the communication in the clinical encounter, screening and prioritising problems, identifying patient preferences that will aid decision-making, monitor changes and response to treatment as well as providing enhanced care to specific population groups such as the one under study (Jaar, Khatib, Plantinga & Powe, 2008).

Research addressing the clinical and cost-effectiveness of measuring HRQoL in conditions such as chronic kidney disease, diabetes and hypertension has reported better health outcomes. Measuring HRQoL in these sub-optimally managed conditions has been suggested to be more cost-effective when compared with conventional management, however evidence of randomized controlled trials is lacking in these types of studies (Black et al., 2010; Howard et al., 2010). A systematic review investigating the cost-effectiveness of anaemia screening in people with underlying illnesses has stated that that there is not enough evidence of screening for decision-making.

However, data comparison is limited by the heterogeneity of these studies (e.g. different types of conditions), demographic factors (e.g. different age groups) and sampling issues (e.g. not using healthy participants as a comparison group), (Nosratnejad, Barfar, Hosseini, Barooti & Rashidian, 2014). A structured review and gap analysis against UK national screening criteria was conducted to investigate whether the prevalence of iron deficiency anaemia could be reduced through a national screening programme. Research evidence has suggested that even though most studies assessed the haematological status of anaemia, there was not sufficient evidence regarding the evaluation of clinical consequences (Rukuni, Knight, Murphy, Roberts & Stanworth, 2015). There is no research addressing the clinical and economic benefits of improved primary care for patients suffering with B₁₂ deficiency and pernicious anaemia. Evidence shows that treatment of B₁₂ deficiency in targeted groups may significantly improve prognosis. Studies with elderly people have suggested daily B₁₂ therapy to normalise the metabolic status and improve neurological symptoms, however, there is still a propensity to misdiagnose B₁₂ deficiency (Iqtidar & Chawdary, 2012).

A better understanding of B₁₂ deficiency, where evidence is lacking, is essential to improve health outcomes particularly in preventing the associated risks resultant from a delayed diagnosis. Although, the availability of new biomarkers may be promising, the disease burden is still not fully addressed. Therefore, it seems plausible to introduce complementary psychosocial screening in this population group aiming to detect the extent to which illness severity impairs HRQoL. This would possibly enable evaluating and treating individual cases.

There is a clear need for timely responses to address the management of PA. Early PA screening and individualised treatment would potentially reduce the economic costs of untreated disease in an already over-stretched health system (Wouters, O' Donoghue, Ritchie, Kanavos & Narva, 2015; Higginson & Carr, 2001).

There is no available patient-centred measure that allows clinicians to understand the health status and treatment benefits of individuals suffering with PA. This thesis aims to fill this gap in response of a tool that can be used in clinical health research to assess the severity of patients' symptoms, therefore enhancing health-related quality of life. This tool will be grounded in the perspective of those living with PA.

Chapter 3

Study 1: Investigating the demographic profile of patients suffering with B₁₂ deficiency: An exploratory audit of patients' records

3.1 Study aims

To investigate the clinical variables that may be relevant for establishing the parameters for developing a patient-centred health-related quality of life measure to assess the severity of patients' symptoms.

3.2 Background

Pernicious Anaemia (PA) represents an autoimmune condition with a chronic course that can have serious implications for sufferers and for medical managers. Patients experience a range of symptoms with differing degrees of severity including extreme tiredness, pins and needles and gait disturbances. Psychological symptoms may include depression, negative affect, cognitive problems and inability to cope with daily living. However, if timely diagnosed and effectively managed, it can lead to a better prognosis. It is anticipated that the development of a patient-centred outcome measure to identify and manage HRQoL will prove valuable for both patients and clinicians. This instrument may provide information regarding individuals' health status, allowing for adjusting the treatment according to patients' needs. This may result in the improvement of patients' symptoms and subsequently improved illness adjustment. The clinical features of PA may manifest in the absence of anaemia or low B₁₂ status (Devalia, Hamilton & Molloy, 2014; Quadros, 2010). When untreated, PA may cause permanent neurological impairment even in the presence of adequate dietary intake (McCaddon, 2013; Langan & Zawitoski, 2011; Bupa, 2008).

Evidence from case studies describes patients suffering from severe neurological manifestations for a long period because B₁₂ deficiency was not included in the differential diagnosis from their primary care physicians (Ralapanawa, Jayawickreme, Ekanayake & Jayalath, 2015; Pacholok & Stuart, 2011). These include paralysis (Matrana, Gauthier & Lafaye, 2009), sub-acute combined degeneration (Paul & Reichard, 2009), gait and balance disorders (Malizia, Baumann, Chansky&Kirchhoff, 2010), paraesthesia and numbness (Wong, Van Spall, Hassan, Coret-Simon, Sahlas & Shumak, 2008; Kumar, 2004), ataxia (Celik, Barkut, Oncel& Forta, 2003) and impaired cognitive functioning (Madksi & Kadrie, 2009).

It is estimated that PA affects approximately 0.1% of the general population and 1.9% of individuals over the age of 60 years (Andrès & Serraj, 2012). However, there is limited research in terms of the prevalence of PA in the UK. Early studies investigating the prevalence in Great Britain, diagnosed locally by blood examination, reported prevalence rates between one per thousand cases to over two per thousand cases in different locations.

In general, the prevalence was 1, 27 per thousand cases (Scott, 1960). The prevalence of B₁₂ deficiency has proven difficult to estimate since existing reports are based on values according to inclusion criteria set by different laboratories (Devalia, Hamilton & Molloy, 2014; Hunt, Harrington & Robinson, 2014; Langan & Zawistoski, 2011; Thorpe, Heath, Blackmore, Lee, Hamilton, O'Broin, Nelson & Pfeiffer, 2007). B₁₂ deficiency may be influenced by demographic factors such as age, gender and ethnicity.

The incidence of B₁₂ deficiency has been proposed to increase with age with the elderly population being more likely to develop B₁₂ deficiency through malabsorption or malnutrition (Hinds, Johnson, Webb & Graham, 2011; Evatt et al., 2010; Stabler & Allen, 2003; Carmel, Green, Rosenblatt & Watkins, 2003). However, there is evidence to suggest that the occurrence of B₁₂ deficiency in young adults may be comparable to that of older adults and that PA may be underdiagnosed in the elderly as well as in younger patients (Allen, 2009; Hershko, Ronson, Souroujon, Maschler, Heyd & Patz, 2006; Clark & Grimley, 2004, Carmel, 1996). Early research has suggested PA to be more common in females in comparison to males (Wintrobe, 1981, Carmel, 1996). However, more recent studies conducted with patients from the United States, Japan, Turkey and Italy, didn't find gender differences in the diagnosis of PA (Lahner & Annibale, 2009; Zittoun, 2001).

Recent epidemiological studies investigating the potential impact of ethnicity in the development of pernicious anaemia have reported higher prevalence in black and Latin American individuals (Carmel, 1996). However, PA diagnosis has been suggested to be prominent in Italy, the United States, Japan & Turkey (Scarpa et al., 2013; Lee-Guzman et al., 2011; Oh & Brown, 2003; Takasaki et al., 2002; Kocak & Paydas, 1992). This may be explained by differences in the genetic background, diagnostic practices and awareness of this condition in different countries. Nevertheless, there is a paucity of research to support the true impact of demographic factors in relation to B₁₂ deficiency and the distribution of PA among different ethnic groups is not clear (Allen, 2013; IOM, 1998, as cited by Evatt et al.,2010).

Autoimmune profiles carried out in individuals suffering from other autoimmune disorders may reveal antibodies, which may be associated with PA, increasing the chances of co morbidity in these patients (Osborne & Sobczyńska-Malefora, 2015). Although there are no clear guidelines proposing PA screening in individuals suffering from other autoimmune disorders, epidemiological research supports their coexistence with PA (Bizzaro & Antico, 2014; Zulfiqar et al., 2014; Lahner & Annibale, 2009). These include thyroid disorders (Toh,2017;Osborne & Sobczyńska-Malefora, 2015; Poye et al., 2014; Ness-Abramof,2006; Weetman, 2005; Antonijević, Nesović , Trbojević & Milosević,1999; Irvine, Davies, Delamore ,Teitelbaum & Williams, 1962; Carmel & Spencer, 1982), type 1 diabetes mellitus (Angelousi & Larger, 2015;Pinto, Dantas, Araujo, Barone, de Souza Papi, Egídio de Oliveira, Zajdenverg & Rodacki, 2013; Thrasivoulos et al.,2009; De Block, De Leeuw & Van Gaal, 2008; Perros, Singh, Ludlam & Frier, 2000) and vitiligo (Gill et al.,2016; Ezzedine, Sheth, Rodrigues, Eleftheriadou, Harris, Hamzavi& Pandya, 2015). Other chronic conditions that have been also found to manifest in individuals presenting with PA include multiple sclerosis (Deleva, Tzoukeva, Kaprelyan & Drenska, 2012; Kocer, Engur & Yilmaz, 2009; Reynolds & Linnell, 1991) and Addison's disease (Bizzaro & Antico, 2014; Alkhateeb et al., 2003; Dittmar & Kahaly, 2003; Zelissen et al., 1995). PA sufferers have also been found to be at a higher risk of developing gastric cancer and carcinoid tumours (Boursi, Mamtani, Haynes & Yang, 2016; Wu, Chen & Lin, 2005; Annibale et al., 2001; Kokkola, Sjoblom, Haapiainen, Sipponen, Pulakkainen & Jarvinen, 1998; Correa, 1992; Sjöblom, Sipponen, Miettinen, Kronen & Jarvinen, 1993).

Studies have reported the annual incidence of gastric cancer ranging approximately from 0.1% to 0.5% in these patients (Kokkola et al., 1998; Schafer, Larson, Melton, Higgins & Zinsmeister, 1985, as cited by Lahner & Annibale, 2009). A survey completed by 889 members of the Pernicious Anaemia society has reported PA co-existing diagnoses. These mainly included depression (45%), tinnitus (34%) and folic acid deficiency (23%) (Hooper, Hudson, Porter & McCaddon, 2014). Nevertheless, despite the potential link between the conditions above-mentioned and pernicious anaemia, studies undertaken have not been able to identify why this may happen. What is certain is the burden caused by PA and associated co morbidity and the restrictions on an individual's quality of life (Hooper, Hudson, Porter & McCaddon, 2014).

One of the major problems in diagnosing B₁₂ deficiency stems from the fact that there are no 'gold standard' tests that provide a clear clinical picture of the deficiency. This becomes a problem when its features are in discordance with test results (Devalia, Hamilton & Molloy, 2014; Berg & Shaw, 2013; Herrmann & Obeid, 2013; Willis, Elshaug, Milverton, Watt, Metz & Hiller, 2011; Devalia, 2006). Although the serum B₁₂ remains the first-line test to investigate B₁₂ deficiency, this test lacks in specificity and sensitivity to successfully diagnose PA (Devalia, Hamilton & Molloy, 2014; Hooper, 2012; Pacholok & Stuart, 2011; Devalia, 2006). The anti-intrinsic factor antibody test (IFAB) is generally carried out in individuals presenting with low serum B₁₂, and in the majority of cases (95%) a positive IFAB identifies PA with high specificity (Devalia, Hamilton & Molloy, 2014).

However, this test has low sensitivity, being accurate in only 40-60% of the cases. Therefore, a negative test outcome may not rule out PA (Wainwright, Narayanan & Cook, 2015; Carmel & Agrawal, 2012; Toh, van Driel & Gleeson, 1997).

A further problem relates to subclinical deficiency, low serum B₁₂ with no evidence of clinical symptoms. Subclinical B₁₂ deficiency restricts prognosis and the identification of health consequences due to its unknown causes in approximately 60% of the cases (Devalia, Hamilton & Molloy, 2014; Carmel, 2012). This represents a key problem that may result in the suboptimal management of PA.

The treatment of Pernicious Anaemia involves the administration of cobalamin in its various forms (methylcobalamin, cyanocobalamin, hydroxocobalamin and adenosylcobalamin) and it takes into account factors such as the cause of the deficiency, treatment toleration and individual variability in absorption (Andrès et al., 2014; Devalia, Hamilton & Molloy, 2014; Stabler, 2013; Andrès & Serraj, 2012; De Paz et al., 2005; Lane & Rojas-Fernandez, 2002). There is no cure for PA, although continuous cobalamin replacement may result in the cessation of anaemia related symptoms. Currently, there are no tailored guidelines for patients suffering with PA that need more frequent B₁₂ therapy.

Expert consensus in the UK, suggest treatment to be initiated with hydroxocobalamin injections, anticipated as being more effectively absorbed and metabolised (Devalia, Hamilton & Molloy, 2014). According to the British National Formulary (BNF), initial treatment for patients without neurological involvement consists in receiving loading doses of B₁₂ to build up the levels of the vitamin, three times a week for two weeks.

Patients presenting with neurological symptoms should receive B₁₂ treatment on alternative days until there is no further improvement. Maintenance treatment typically includes lifelong intramuscular hydroxocobalamin injections (1000 µg) between one and three months for patients with neurological deficit and without neurological deficit (Devalia, Hamilton & Molloy, 2014). Despite receiving regular treatment, many patients perceive the need of taking more frequent B₁₂ therapy due to relapse of symptoms before the next treatment is due. While the administration of more intensive therapy is at times at the discretion of the health professional, some GPs decline more frequent treatment since they may be concerned with early medicalisation in mild and transient cases, when there is no demonstrated clinical benefit (Andrès, Fothergill & Mecili, 2010; Carmel, 2008; Nyholm et al., 2003; Lane & Rojas-Fernandez, 2002).

The absence of objective markers to successfully diagnose PA means that patient care is compromised. A delay in the diagnosis of PA may result in the progression of illness and subsequent reduced health-related quality of life, resulting from the inadequate management of symptoms. Hence, developing the HRQoL instrument may potentially supplement existing approaches to the management of this complex condition.

Pernicious anaemia represents a condition with slow onset and progression. Clinical management should involve prompt diagnosis, effective treatment and monitoring to prevent the long-term consequences associated with this condition. Therefore, understanding the health care needs of this population is key to effective PA management.

Since there is very little existing research into this condition, the present audit aims to identify key issues and variables of importance regarding the diagnosis and treatment of PA, guiding the structure of the subsequent studies that form the current thesis.

3.3 Methodology

3.3.1 Design

This study involved an exploratory design in the form of an audit. The use of electronic health recorded data for research purposes is part of clinical governance. The Quality Care and Clinical Excellence (Welsh Office, 1999) has defined clinical governance as “a framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care, by creating an environment in which excellence in clinical care will flourish”.

Patient recorded information included demographics and clinical data. The variables recorded included, age, gender, ethnicity, marital status, offspring information, occupation, PA family history, types of tests conducted to diagnose B₁₂ deficiency/PA, B₁₂ therapy type and frequency, time since diagnosis, consultation history, diseases, signs and symptoms, B₁₂ therapy and information related to haematology and gastroenterology referrals. Patients' records were inspected for a period of approximately five months.

3.3.2 Ethical considerations

The Research and Development Committee in the Abertawe Bro Morgannwg University Health Board (ABMU) was approached for advice and it was agreed that for the present study, Local Research Ethics Committee review (LREC) was not required. Subsequently, a local GP practice in the area of Bridgend agreed to enable access to patients' records. The data collection period started in April 2010 and ended in August 2010.

After the data collection period, approval was granted from the GP practice for the research team to make use of the data as required (Appendix 1). The University of South Wales (USW) granted ethical approval for the present study. Confidentiality was maintained for any published data. The confidentiality and management of medical data was ensured, in compliance with the Data Protection Act (1998) and BPS guidelines (2010). Patient identifiable information was anonymized and computer files were encrypted. Paper records were retained in a secure access-restricted storage cabinet, password-protected and only accessible by the research team.

3.3.3 Sample

Existing routinely collected data was recorded for all patients (Appendix 2) recorded as receiving B₁₂ therapy (N=257, 189 females, 68 males, age range 25-97 years old, mean age= 65, SD=17). This sample included 87 patients diagnosed with PA and 135 patients diagnosed with B₁₂ deficiency. Records regarding 35 patients suggested as receiving B₁₂ therapy did not specify why this was the case. Therefore, data from these participants were excluded from the analyses. The final sample consisted of 222 participants.

3.3.4 Materials

The Database, Egton Medical Information System (EMIS) was accessed. Currently known as EMIS Health, represents one of the UKs leading clinical systems IT supplier. This database is used by a great number of healthcare organisations, from GP practices and out-of-hours services, to community services. This system enables health professionals to access the same information about their patients by supporting integrated care (EMIS group, 1987, 2015).

3.3.5 Procedure

Access to the EMIS database was facilitated by the manager of the GP practice in the Bridgend area. Records of all the patients recorded as receiving B₁₂ therapy were scrutinized. Patient data was initially recorded as specified in the medical records. Information included patient demographics and clinical data. After the data collection period ended (April 2010-August 2010), all of the variables were recorded into a password-protected database. Data confidentiality and security followed the University of South Wales's guidelines in compliance with the Data Protection Act (1998), NHS Caldicott Guardian (department of health; DH, 2003) and The Research Governance Framework for Health and Social Care (DH, 2005).

3.4 Results

Prior to analysis, disease and signs and symptoms' data were categorised by type (Appendix 3) using the 10th revision of the international statistical classification of diseases and related health problems (ICD-10). The ICD-10 has been recommended as a valuable tool, capturing quality data, aiming to improve diagnostic procedures and disease management (Bowman, 2008). This classification system comprises of codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases (WHO, 2010).

3.4.1 Descriptive analyses

Patient recorded data included demographics and clinical data. The variables recorded included, age, gender, ethnicity, marital status, offspring information, occupation, PA family history, haematology and gastroenterology referrals, types of tests conducted to diagnose B₁₂ deficiency/PA, B₁₂ therapy type and frequency, time since diagnosis, consultation history, signs and symptoms and diseases. Data was checked for normality prior to computing descriptive analyses.

The Shapiro-Wilk test was employed as numerical means of assessing normality for the variables of 'age and 'gender' in relation to a PA diagnosis. This test is appropriate to use in small sample sizes <50 (Field, 2009).

The data collected indicated that the variable 'age' did not fit the normal distribution. The observed value of the Shapiro-Wilk ($W=0.966$) and the exact probability of the outcome was statistically significant ($p=0.000$), with skewness of -0.37 ($SE=0.16$) and Kurtosis of -0.77 ($SE=0.32$).

This may be explained by the age of diagnosis where the typical onset has been suggested to be over the age of 60 years for both males and females (Hinds, Johnson, Webb & Graham, 2011).

For the variable 'gender', the observed value of the Shapiro-Wilk ($W=0.548$, $p=0.000$) indicates that the PA diagnosis according to gender is non-normally distributed, with skewness of -1.09 ($SE=0.16$) and Kurtosis of -0.81 ($SE=0.32$). A possible explanation refers to the uneven distribution in gender in relation to the diagnosis of B₁₂ deficiency/PA weighing towards females.

The above values indicate that the data deviates from the normal distribution in age and gender according to the diagnosis of PA/B₁₂ deficiency. This seems to fit the distribution for this population, where diagnoses seem to be more common in females and in older individuals. However, it may be argued that this sample is partly representative of the PA population, since there is mixed evidence regarding the predominance of a PA diagnosis in females (Hooper, Hudson, Porter & McCaddon, 2014; Lahner & Annibale, 2009; Zittoun, 2001 Carmel, 1996; Wintrobe, 1981).

Normality was further explored for the remaining variables in the study to investigate potential data skewness. The data also deviates from normality for the other recorded variables. It has been previously suggested that audit data often reflects skewed distributions due to the inaccuracies in record-keeping (Federay, 2006).

3.4.1.1 Characteristics of the population under study

Patients' records (N=257; 189 females, 68 males; Mean age = 65.5 years old, SD=17.1) indicated that the majority of the population was White British (79%). Only a small proportion of the population were Asian (1.2%), Irish (0.4%) and Italian (0.4%). There was no information regarding the ethnic background for 19% of the cases. More than half of the sample was married (55.6%), 25.7% were recorded as living alone, 7.4% were widows and 2.3% were recorded as living in a nursing home. Marital status indicated that 5.8% of the population were single, 1.6% divorced and 1.6% living in partnership. Further, 45.5% of the patients were recorded as having offspring. Patients' records regarding 'occupation' were only available for 9% of the population and mainly included occupations in the areas of education, hospitality and healthcare.

3.4.1.2 Clinical data

The diagnoses of B₁₂ deficiency and Pernicious Anaemia were reported in 52.5% (n=135) and 34% (n=87) of the cases, respectively. There were no diagnoses of B₁₂ deficiency or Pernicious Anaemia in 13.5% of the cases (n=35). Although these patients (n=35) were recorded as receiving B₁₂ therapy, it was not clear why this was the case. For the effect, data regarding these patients were removed from the analyses. Descriptive analyses were computed for the remaining records of patients diagnosed with PA/B₁₂ deficiency (n = 222).

Family history of PA for these patients (n = 222) was recorded for 8.1% of the individuals. Referrals to haematology were recorded for 26% of the cases and in 6% of the cases, referrals were made to gastroenterology. Time since diagnosis varied from 1 year to 25 years, being the most common 5 years (15%). The number of consultations per year varied from 1 to 23 consultations/year, being the most common 3 consultations/year (23%).

Data was further inspected to investigate the prevalence of B₁₂ deficiency and PA in different age groups (table 3.4.1.2).

Table 3.4.1.2

The prevalence of B₁₂ deficiency and Pernicious Anaemia in different age groups (n = 222)

Prevalence	Age groups (yrs.)							Total (%)
	25-34	35-44	45-54	55-64	65-74	75-84	85-97	
B₁₂ deficiency (n=135)	5.9	7.4	14.8	15.6	20.7	23	12.6	100
PA (n=87)	6.9	10.3	15	16.1	20.7	19.5	11.5	100

The above table shows some similarity in the prevalence of both diagnoses across different age groups. The above table seems to indicate a higher prevalence of both diagnoses, increasing with age up until the age of 74 yrs. old. However, a decline is observed in older patients. This may suggest that these conditions may be missed in the elderly population or due to the likely occurrence of death in older population groups (Iqtidar & Chaudary, 2012; ONS, 2012).

3.4.1.3 Diagnostic testing

Testing undertaken to achieve a diagnosis of B₁₂ deficiency/PA indicated that the serum B₁₂ test was carried out in 61% of the cases and the complete blood count in 18.4% of the cases. Further tests aimed at detecting B₁₂ deficiency, the intrinsic factor antibody test and gastric parietal cell test were carried out to a lesser extent in 12.6% and 11.1% of the cases, respectively. The main tests conducted to diagnose PA/B₁₂ deficiency are displayed below (Fig.3.4.1.3)

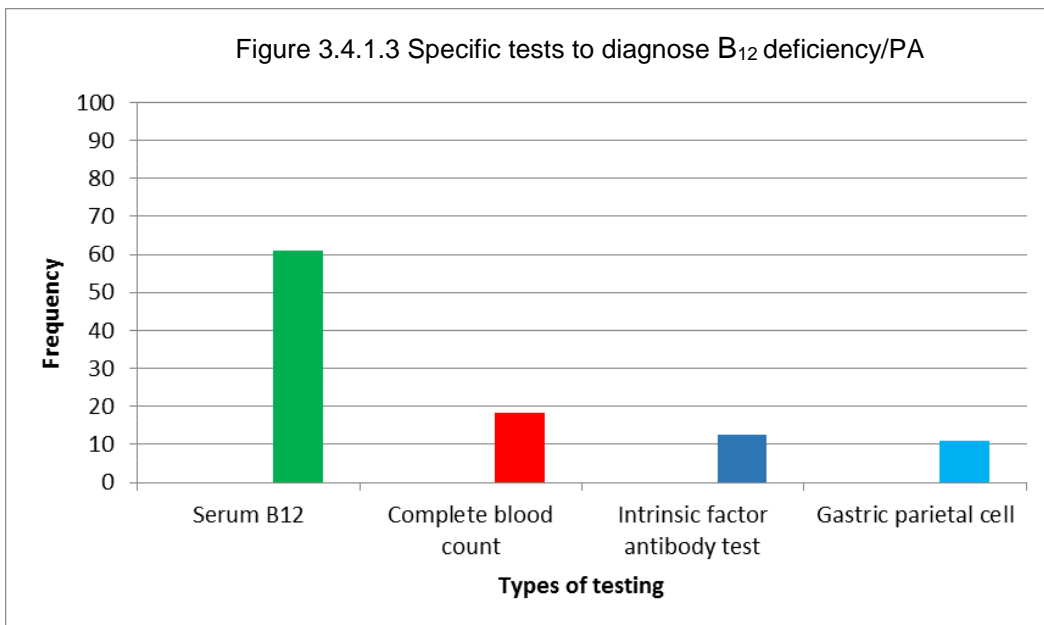


Figure 3.4.1.3 Main tests carried out for the diagnosis of B₁₂ deficiency/PA

3.5 Signs and symptoms

Patients experienced general signs and symptoms in 37% of the cases, signs and symptoms involving the respiratory and circulatory systems (37%), involving the digestive system and abdomen (27%), involving cognition, perception, emotional state and behaviour (24%), skin and subcutaneous tissue (12%) and signs and symptoms involving the nervous system (11%).

Signs and symptoms were broken down to include the most common signs and symptoms within each category. The main signs and symptoms experienced are presented in the graph below (Fig.3.5.1)

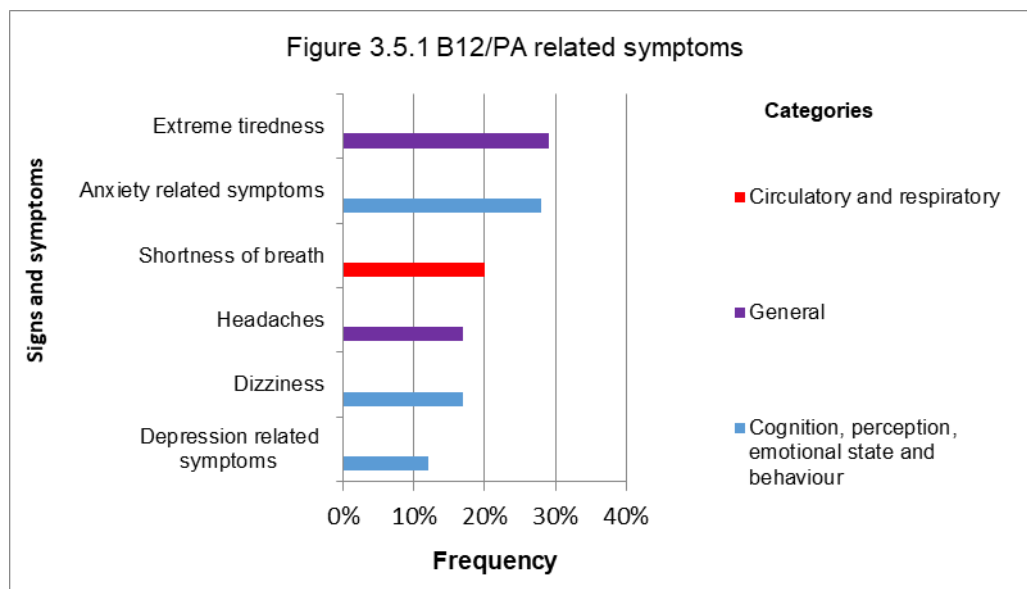


Figure 3.5.1 Most common types of signs and symptoms recorded in patients' diagnosed with B₁₂ deficiency/PA.

This figure shows that extreme tiredness (29%), anxiety state (28%) and shortness of breath (20%) were the most common symptoms experienced in this population, followed by headaches (17%), dizziness (17%) and depression related symptoms (12%). These symptoms have been previously suggested to be linked to a diagnosis of PA/B₁₂ deficiency (NIH, 2011).

3.6 Co-morbid diseases

Generally, the main conditions that individuals presented related to diseases of the musculoskeletal system and connective tissue (34%), digestive system (34%), circulatory system (26%), skin and subcutaneous tissue (24%), genitourinary system (24%), mental and behavioural (23%), nervous system (23%), respiratory system (21%) and eye and adnexa (18%).

Disease categories were broken down to include the main diagnoses that formed each category. The main conditions experienced are presented in the graph below (Fig.3.6.1).

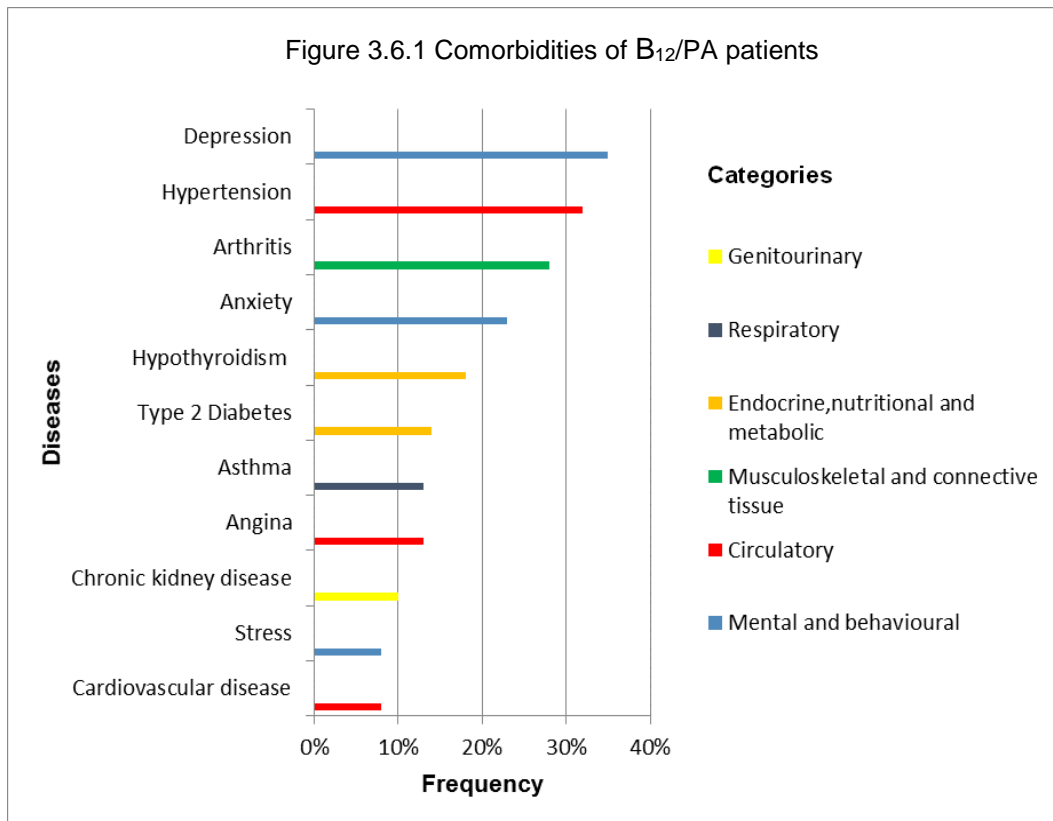


Figure 3.6.1 Most common types of co-existing conditions recorded in patients diagnosed with B₁₂ deficiency/PA.

The above graph indicates that depression was one of the most common co-existing conditions (35%) followed by hypertension (32%), arthritis (28%) and anxiety (23%). Other conditions included hypothyroidism (18%), angina (13%) and stress (8%). However, it is not clear the link between these conditions and the development of PA/B₁₂ deficiency.

3.7 B₁₂ therapy type and frequency

B₁₂ treatment was recorded as being administered regularly (between 1 -3 months) in 87% of the cases and intermittent in 2.3% of the cases. Other frequencies of treatment related to every four months (0.9%). Regarding the type of B₁₂ therapy, a great majority of the patients were receiving B₁₂ in the form of injections (95.9%).

Data were further explored to investigate records of patients in regular receipt of cobalamin therapy (1-3 months), (N = 193, M = 64 years old, SD = 17.4). This population was composed of 144 females with ages ranging from 25 to 97 years old (M = 61.7, SD = 18.3) and 49 males with ages ranging from 36 to 93 years old (M = 71, SD = 11.8). The table below presents key characteristics of these patients (Table.3.7.1)

Table 3.7.1

Key characteristics of patients diagnosed with PA/B₁₂ deficiency in regular receipt of B₁₂ therapy

Patient characteristics (n=193)	Absolute frequency (n)	Relative frequency (%)
Background (White British)	149	77%
Specific diagnostic testing	30	16%
Haematology referrals	23	12%
Gastroenterology referrals	13	6%
PA family history	6	3%

The above table shows that the majority of this population was White British (77%) 12% of these patients were referred to haematology and PA family of history was recorded in 3% of the cases.

Specific diagnostic testing was recorded as being carried out in a small proportion of the population (16%). The diagram below shows the flow of patients undergoing specific diagnostic testing (Figure 3.7.1)

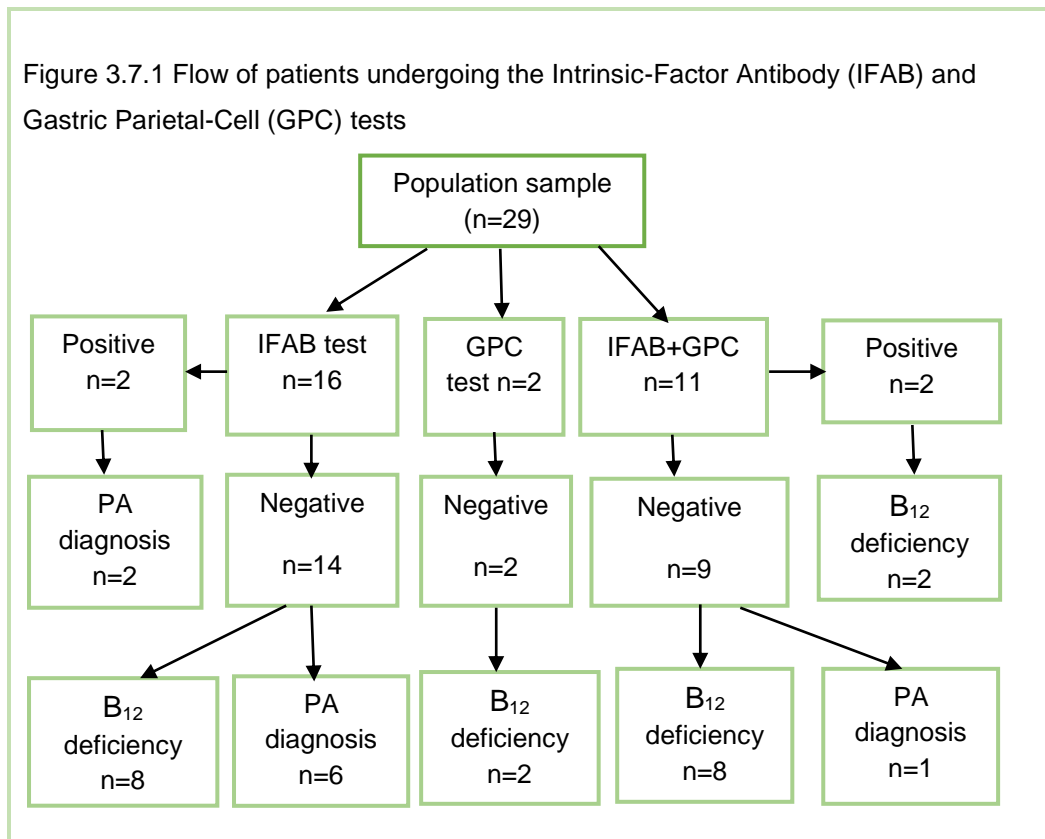


Figure 3.7.1 Specific tests carried out to diagnose B₁₂/PA. Generally, a positive IFAB result will be indicative of PA. Combining the IFAB and GPC results will strengthen laboratory findings (Devalia, Hamilton & Molloy, 2014). However, a negative IFAB result will not rule out PA (Carmel, 2008; Hooper, Porter & McCaddon, 2014).

The flow chart suggests that for 12% of patients who underwent IFAB testing (n=23) only 2% (n=4) received an accurate PA diagnosis, signified by the positivity of the test.

However, in some cases where the IFAB was negative patients were still diagnosed with PA. This may reflect variations in the management of PA, which may potentially be determined by the lack of accuracy in diagnostic testing (Hooper, Porter & McCaddon, 2014).

3.8 Signs and symptoms

Table 3.8.1

Signs and symptoms recorded in patients diagnosed with PA/B₁₂ deficiency in regular receipt of B₁₂ therapy

Signs and symptoms(n=193)	Frequency (%)
Extreme tiredness	27%
Shortness of breath	21%
Dizziness	16%
Depression related symptoms	12%
Confusion	6%

Table 3.8.1 suggests extreme tiredness, followed by shortness of breath and dizziness as the most common symptoms present in this population. To a lesser extent, depression related symptoms and confusion were recorded as being experienced by these patients.

3.9 Diseases

Table 3.9.1

Diseases recorded in patients diagnosed with PA/B₁₂ deficiency in regular receipt of B₁₂ therapy

Diseases(n=193)	Frequency (%)
Depression	36%
Arthritis	28%
Anxiety	22%
Type 2 diabetes	16%
Dementia	8%

The table above shows the predominance of depression in these patients, followed by arthritis, anxiety and type 2 diabetes and to a lesser extent, dementia. This section has outlined the demographic profile of patients diagnosed with PA/B₁₂ deficiency by focusing on patient characteristics and clinical information. Implications of these results will be discussed in the next section.

3.10 Discussion

The aim of the present study was to investigate the progression of patients diagnosed with B₁₂ deficiency, from diagnosis through treatment and management of the condition. Results of the present study were useful in terms of providing information regarding the demographic profile of these patients as well as to further highlight what appear to be inconsistencies with the management of PA. These mainly include clinical investigations that appear to be carried out to a lesser extent than it would have been anticipated.

Patients' records indicated that the diagnosis of B₁₂ deficiency seemed to increase with age. While there is no recent research documenting the true prevalence of B₁₂ deficiency in the UK, previous studies conducted suggest a higher prevalence of PA in the older population (Hinds, Johnson, Webb & Graham, 2011; Evatt et al., 2010). However, findings also show a decline in the prevalence of B₁₂ deficiency and PA at a later age (75 years old onwards), potentially suggesting that B₁₂ deficiency may be underdiagnosed in the elderly (Iqtidar & Chaudary, 2012; Allen, 2009). This may also be related to other factors such as subclinical B₁₂ deficiency (O'leary & Samman, 2010), no routine screening for nutritional deficiencies in the elderly (Hanna, Lachover & Rajarethiram, 2009) or the association with other conditions that may mask the presence of B₁₂ deficiency (Herrmann, Lorenzl & Obeid, 2007; Russel & Baik, 2001).

Previous research has also suggested that the occurrence of PA/B₁₂ deficiency in young adults may be comparable to that of older adults (Allen, 2009; Hershko et al., 2006); however, this is not clearly reflected in the current findings. However, it may also be the case that these diagnoses are potentially missed at an earlier age. It has been previously stated that PA/B₁₂ deficiency manifestations appear to be non-specific, presenting as developmental delays in children and adolescents (Goraya, 2002; Rasmussen, Fernhoff & Scanlon, 2001).

PA/B₁₂ deficiency was shown to be more prevalent in females in comparison to males. Whilst early studies (Wintrobe et al., 1981; Carmel, 1996) have supported gender predominance in these conditions, other studies suggest that this may not be the case (Lahner & Annibale, 2009; Annibale et al., 2000; Sarit et al., 2000; Haruma et al., 1995). It is unclear what pathogenic mechanisms may explain this difference, although, behavioural gender differences in seeking health care may constitute one possible explanation for the results of the study, as literature suggests that women are more likely to report health complaints in comparison to men (Schmetzer & Florcken, 2012; Regitz-Zagrosek, 2012; Zandman-Goddard et al., 2012). Previous studies addressing gender differences in health care utilization, have suggested the higher frequency of somatic morbidity and poor perceived health status as the main reasons for women seeking help to a higher extent than men (Koopmans & Lamers, 2007; Mackenzie, Gekoski & Knox, 2006; Lahelma et al., 1999). However, the link between somatic morbidity and gender-based misdiagnoses is scarce.

Available research that may partly support this is mainly qualitative and refers to misdiagnoses of psychological distress occurring in women presenting with chronic fatigue syndrome and fibromyalgia (Åsbring & Närvänen, 2002).

Although studies suggest a strong genetic predisposition in the development of the PA (Banka, Ryan, Thomson & Newman, 2011; Conrad, 2009; Wangel, Callender, Spray & Wright, 1968 Wittingham, Mackay, Ungar & Mathews, 1969 Callender and Denborough, 1957), family history was only recorded for a small proportion of the population. Therefore, records in the present study were not indicative of a strong genetic link.

Guidelines for the management of B₁₂ deficiency in primary care (Grey, Wright & Athar, 2015) based on expert consensus, propose that referrals are generally determined by the cause of B₁₂ deficiency. Referrals to haematology are usually forwarded in cases where patients may be pregnant, present with neurological symptoms or the cause of B₁₂ deficiency is unclear. In other cases such as suspected malabsorption, patients are referred to gastroenterology (Kuipers, 2015; NICE, 2013). In the present study, only a small proportion of patients were referred to haematology and an even smaller proportion were referred to gastroenterology. However, it is unknown whether this could be potentially related to poor practice or no perceived need to further investigate these patients.

However, screening for B₁₂ deficiency may not be on the health professionals' radar. Initial investigations may only include a full blood count and serum B₁₂ may not be routinely requested (Hooper, 2015). On a positive note, findings from this study indicated that the serum B₁₂ test was requested in the majority of cases. According to the NHS Atlas of Variation in Diagnostic Services, serum B₁₂ investigations were requested according to specific areas in England.

Figures of tests ordered per 1000 patients indicated that in certain areas, B₁₂ levels were approximately five times more likely to be investigated when compared to other areas. This may be explained by health professionals relying solely on haematological manifestations, which do not represent an accurate indicator of PA/B₁₂ deficiency (NHS, 2013).

Patients' records indicated that the IFAB was only carried out in a small percentage of the population. Further, negative test results were also indicative of a PA diagnosis, supporting previous research (Wainwright, Narayanan & Cook, 2015; Devalia, Hamilton & Molloy, 2014; Carmel & Agrawal, 2012; Toh, van Driel & Gleeson, 1997). Alternatively, the GPC accounts for positivity in 80% of the cases, it bears low specificity, being also positive in 10% of normal individuals. Thus, findings of the GPC are inconclusive (Khan, Del-Duca, Fenton, Holding, Hirst, Dore & Sewell, 2009). In the present study, GPC single investigations were recorded to a much lesser extent. Findings from a retrospective study have anticipated that in cases of suspected PA, both tests should be measured concurrently since the IFAB tends to manifest in the presence of GPC antibodies (BNF, 2010; Lahner, et al., 2009). This was true for nearly half of the cases, where both investigations were carried out with a positive outcome for PA.

Nevertheless, considering the number of PA/B₁₂ deficiency diagnoses, this was carried out to a lesser degree. In view of this, the extent to which B₁₂ deficiency diagnoses may reflect PA diagnoses may well be questioned.

According to the British National Formulary, test monitoring should be performed to ensure haemoglobin levels are maintained (BNF, 2010). Records in the study do not provide enough data to support that response to B₁₂ therapy was effectively managed. There were gaps in the data regarding how often tests were monitored as well as gaps in the results of haematological investigations. B₁₂ values that would reflect pre and post B₁₂ therapy would have been useful to ascertain if levels were maintained over time (Aktas et al., 2014).

Despite potential caveats in the patients' records, the majority of diagnosed patients were in receipt of B₁₂ therapy, mainly in the form of intramuscular injections, previously suggested as being more effectively absorbed and metabolised when compared to oral treatment (Devalia, Hamilton & Molloy, 2014). For most cases, B₁₂ therapy was also administered on a frequent basis as per expert recommendation (NICE, 2013). One of the main complaints by members of the PAS reflects the need for more frequent treatment to alleviate perceived symptoms (Hooper, Porter & McCaddon, 2014, Devalia, 2006). Whilst there was no way of knowing how many diagnosed patients were also members of the PAS, a very small number (n=12) of GP observations in the patients' records suggested that while patients' perceived improvement in their symptoms since initiating B₁₂ therapy, such as feeling more energetic, some also suggested relapse of symptoms a couple of weeks before treatment was due, feeling fatigued and depressed.

It was interesting to note that there was no documented request for more frequent therapy, even though one patient was advised by her GP to have earlier treatment, due to the severity of symptoms presented.

These observations also indicated patient's perceptions of injections being painful and treatment being discontinued or interrupted without apparent reason, despite PA diagnosis.

It would be very helpful to investigate beliefs on how PA is managed and how it may affect response to treatment. Individuals' beliefs regarding their illness experience have been widely investigated and associated with illness adjustment in conditions such as multiple sclerosis (de Seze, Borgel & Brudon, 2012, Vaughan, Morrison & Miller, 2003) and rheumatoid arthritis (Kumar, Peters & Barton, 2016; Taylor et al., 2010).

The most common symptoms in this study included extreme tiredness and shortness of breath (PAS, 2012) as well as the experience of psychological symptoms such as anxiety and depression (NIH, 2011; Brian & Kelly, 2000). One of most common co-morbidities recorded in this population indicated depression. PA has been previously associated with depression (Milanlioglu, 2011; Hanna, Lachover & Rajarethinam, 2009; Durand, Brazo & Dollfus, 2003). However, most of the studies describing the psychiatric manifestations of PA including depression, delusions and anxiety, emerged from case reports (Mrabet, Ellouzi, Ellini & Mrad, 2015; Carneiro, Couto, Braz & Andrade, 2009; Durand, Brazo & Dollfus, 2003). Findings of an online survey investigating diagnosis and treatment of PA, have suggested depression as one of the main co-existing conditions present in PA patients (Hooper, Hudson, Porter & McCaddon, 2014). This may be not surprising, as depression has been highlighted as one of the most common complications, adversely affecting the course and management of chronic illness (NICE, 2009).

Studies tend to report an increased prevalence of depression in individuals suffering with chronic conditions (Boing et al., 2011; Katon, 2011; Ali et al., 2006). However, it is unclear whether depression in these patients reflects an established diagnosis. Nevertheless, psychological problems need to be addressed. Experiencing chronic illness may affect one's mood and result in distress, making it difficult to cope with illness demands. Other recorded conditions in this study included hypertension and arthritis. While epidemiological research supports the coexistence of PA with other conditions, there is no evidence of a causal link between PA and these conditions (Toh, 2017; Angelousi & Larger, 2015; Bizzaro & Antico, 2014).

While exploratory studies generate quality information, interpretation of such type of information may also be subjected to bias. One reason for this could relate to common errors in record keeping such as not updating patient information. Exploratory studies usually make use of a modest number of samples that may not adequately represent the target population. Further, the present study did not take the form of a clinical audit, in the absence of a rigorous approach to aid implementation of change in clinical practice (NICE, 2013). Although the information presented here may be useful in terms of highlighting ways to improve the quality of patient care, the present audit (survey) was only performed in one local surgery. Further research should focus on scrutinizing the records of different GP practices in different areas in the UK, to provide a better picture of the extent of the problem.

The present study has provided a good insight into the potential issues with the management of B₁₂ deficiency. These issues revolve around poor practices in testing, diagnosis, treatment and record keeping. Further research is required to explore what seem to be inconsistencies in the management of B₁₂ deficiency. The present study is lacking on the patients' perspectives, an important aspect in the assessment of care. Patient-centred measures that consider individual experiences emphasise the meaningful aspects of one's illness. For the effect, the next pilot study will aim to investigate diagnostic and treatment experiences of PA sufferers to help fill the gaps that were highlighted in the current study, leading to a better understanding of PA/B₁₂ deficiency. This may significantly improve current PA practices.

Chapter 4

Study 2: Exploring individuals' perceptions of their PA experience: a small-scale qualitative study

4.1 Study aims

To investigate the diagnostic and treatment experiences of individuals suffering with pernicious anaemia

4.2 Background

Pernicious Anaemia is a chronic condition where clinical diagnosis is difficult to establish, having serious consequences for patients (Carmel, 2008). Patients present with non-specific symptoms, increasing the chances of a delayed diagnosis. This has profound implications in terms of managing one's symptoms, social lives and relationships (Hooper, Hudson, Porter & McCaddon, 2014). Given the issues regarding diagnosis and treatment mentioned in the previous study (study 1), this chapter aims to provide a rationale for the need to include patient perspectives as part of the management of PA. There seems to be a pattern in the literature documenting the experience of chronic illness patients (Pierret, 2003; Thorne et al., 2002). This pattern reflects the journey from the awareness of symptoms to receiving an established diagnosis, negotiating treatment and the acknowledgment of how one's illness disrupts one's identity and relationships, therefore impacting on one's overall quality of life. The provision of information and support is also crucial in this process (Miller & DiMatteo, 2013; Falk, Wahn & Liddell, 2007; Parry, Peel, Douglas & Lawton, 2004).

The following studies investigate the illness experience from diagnosis through treatment and management, in different chronic conditions. These studies document recurrent problematic issues faced by PA patients, such as the experience of delayed diagnoses and the poor provision of healthcare support.

Similar to PA, gout may be difficult to diagnose due to the lack of precise testing. A study by Liddle et al., (2015) has investigated the extent of suboptimal management in this condition, by mapping patients' experiences from initial symptoms to diagnosis. Semi-structured interviews were conducted with 43 British individuals. The main themes that emerged from these narrative accounts included symptom interpretation, decisions to seek health care, diagnostic delays and the meaning of getting a diagnosis. Findings suggested that patients' experience of severe symptoms elicited fear of being diagnosed with a life-threatening condition. Diagnostic delays were influenced by financial pressures, the inability to get timely appointments, self-diagnosis and delayed treatment. In this study, gout patients also expressed lack of confidence regarding the accuracy of their diagnosis. This was linked to preconceptions of a gout diagnosis (e.g. lifestyle). Once diagnosed, patients did not feel that they received enough information and support to be able to deal with gout. Nevertheless, they actively engaged in lifestyle changes and self-monitoring of their condition.

A phenomenological study was employed to understand the experience of 14 individuals living with chronic obstructive pulmonary disease and how this condition affected patients' lives. The main findings emerging from this study related to symptom control, functional disabilities and emotional trauma.

This study highlighted the experience of severe symptoms such as breathlessness resulting in fear and anxiety, reflecting changes in priorities such as avoiding social interaction. Patients also conveyed loss of social roles, frustration and emotional trauma resulting from the need to be reliant on relatives for support (Avşar & Kaşıkçı, 2010).

An earlier study by Cheek and Oster (2002) looked at patients' understanding of living with asthma and diabetes as well as the perception of risks associated with both conditions. Feelings of denial, uncertainty regarding prognosis, feeling stuck with the condition and changing as a person, were highlighted as major concerns by these patients.

In a survey study, individuals reflected on approaching chronic fatigue syndrome from a holistic point of view. The experience of severe symptoms such as breathlessness was suggested to disrupt one's pattern of daily living (Tuck & Human, 1998). Other psychological and social factors that are commonly mentioned by patients as a consequence of living with a chronic condition refer to frustration whilst seeking validation for their symptoms (Swoboda, 2008; Dickson, Knussen & Flowers, 2007), strained relationships (Dejean, Giacomini, Vanstone & Brundisini, 2013; Dickson, Knussen & Flowers, 2007) and the experience of social stigma (Tucker, 2008; Johnson, 2007). However, there is also optimism in these accounts. This relates to positive experiences emerging from diagnosis and treatment, such as accepting the condition and taking control, facilitating one's adjustment (Spessotto et al., 2016; Barton et al., 2009; Cheek & Oster, 2002).

The aforementioned studies provide an insight into the general experience of living with a chronic condition. While there seem to be similar features in terms of the diagnostic process and management of various conditions, individual experiences tend to be overlooked by health professionals (Wilson, 2011; Davis, 2006; Cheek & Oster, 2002). This has implications for clinical practice in terms of developing effective strategies that are patient-centred, and aim to improve patient outcomes. Late diagnosis, dissatisfaction with the treatment regime and distrust in the medical profession has been previously reported in a survey with the members of the PA society. While this survey represents the first published study to date investigating issues with diagnosis and treatment in this population, it does not focus on the psychosocial impact of PA (Hooper, Hudson, Porter & McCaddon, 2014). In the absence of previous qualitative research specifically exploring the experiences of PA diagnosis, study 2 aims to fill this gap by capturing individuals' perceptions of their PA experience by conducting individual semi-structured interviews with a purposive PA sample. Findings from the present study will provide an understanding regarding the variables that may influence the illness experience in this population. This information will build the foundations for the development of the HRQoL instrument.

4.3 Methodology

4.3.1 Design

The present study employed a qualitative design in the form of seven face-to-face semi-structured interviews, aiming to capture in-depth the lived experiences of PA sufferers. Interviews were analysed using thematic analysis, a widely used analytic method in qualitative research, flexible in nature, providing a rich and comprehensive account of the data corpus (Braun & Clarke, 2006). Thematic analysis is a useful method for interpreting and reporting meaningful themes within the data (Boyatzis, 1998). Themes were interpreted using a semantic approach “directed towards understanding informants’ perspectives of their lives, experiences or situations as expressed in their own words” (Taylor & Bogdan, 1984, p.77). The analysis followed six stages outlined by Brown and Clarke (2013; 2006). These recursive stages refer to the familiarisation with the data, coding, the search for themes, reviewing themes, defining themes and the contextualisation of themes.

4.3.2 Ethical considerations

The School of Psychology in the host institution (University of Glamorgan) granted ethical approval. Individuals agreed to be interviewed and provided their verbal consent to participate in the interviews. At the start of the interview, participants were informed of the purpose and aims of the research being carried out. The researcher asked for permission to use their accounts for purposes of research dissemination, ensuring data anonymity and confidentiality. Participants were also informed of their right to withdraw from the research at any time. Data were stored according to the university guidelines in accordance with the British Psychological Society (2010).

4.3.3 Sample

The present study represented a sub-sample of 7 individuals who had received a formal diagnosis of PA, recruited through an advert posted online in the University of Glamorgan intranet (Appendix 2.1). These participants were purposefully selected, aiming to achieve information-richness (Oliver, 2011). Seven participants were interviewed (6 females, 1 male; age range 21-58 years old). All participants lived in the Cardiff area. Family history of PA was recorded for six of the participants.

4.3.4 Materials

Data collection was guided through a semi-structured interview schedule that included open-ended questions. This interview guide was developed based on a comprehensive review of the PA literature and informed by the need to further explore the issues that were highlighted in study 1, such as the experience of diagnosis, provision of health information and treatment. Central questions in the interview guide related to the understanding of the condition, beliefs regarding treatment, symptom perception, locus of control and quality of life. These questions were discussed by members of the wider research team and were pilot tested in an individual suffering with pernicious anaemia. This allowed for the refinement of the interview schedule ensuring relevant content and structure. Questions asked included 'can you please describe the process leading up to the diagnosis of PA?', 'when diagnosed, did you feel that you were informed by your GP about your illness? Was this information beneficial?' and 'did you ever have a break on the course of your treatment?'(Appendix 2.2).

Participants were encouraged to be open about their experiences of living with PA. Interviews were recorded using a Sony voice recorder (V.1.1.1) and data were transcribed verbatim of audio-recordings.

4.3.5 Procedure

An advert requesting PA sufferers to share their experience of living with the condition was posted in the University of Glamorgan's intranet (Appendix 2.1). After responding to the advert, participants were interviewed in their place of choice. This included their home environment (5 out of 7) or their workplace (1 out of 7) and lasted an average of 30 min each. The accuracy of the transcripts was checked against the recordings a few times, to ensure familiarity with the material before transcription. Interpretive challenges regarding the transcription in textual form were minimised as the researcher checked for potential errors several times against the recordings (Poland, 2002). Identifying information was removed from the transcripts and replaced with identifiers attached to each quote (gender, age and line number). After transcribing the interviews, transcripts were read several times to identify meaningful patterns within the data. These units of meaning were assigned to a theme and relevant sub-category. Transcripts were read and analysed by a second researcher to both challenge and finally achieve inter-coder agreement, as recommended by Braun & Clarke (2006) and Denzin & Lincoln (2005). After reaching a consensus, themes were revised and re-arranged into sub-categories.

4.4 Research findings

This section includes the main characteristics of the population under study and the outcome of the analyses of the semi-structured interviews.

The sample includes 7 PA sufferers, 6 females and 1 male with ages ranging from 21 to 58 years old. The main characteristics of this population are described in the below table (table 4.4.1).

Table 4.4.1

Demographic characteristics of PA sufferers

Interview/individual no.	Age	Gender	Ethnicity	MS	FH(relatives)	AD(years)	Comorbidities
Individual 1	25	Female	White British	Married	Grandmother	18	None
Individual 2	49	Female	White British	Married	Grandmother, father, sisters and nephews	42	Underactive thyroid
Individual 3	21	Female	White British	Single	Grandmother, mother, aunt and cousins	18	None
Individual 4	55	Male	White British	Married	Parents and brother	39	None
Individual 5	38	Female	White British	Single	No FH	38	Asthma
Individual 6	56	Female	White British	Married	Mother	43	Underactive thyroid and rheumatoid arthritis
Individual 7	58	Female	White British	Married	Mother	54	High blood pressure

Note. MS =marital status; FH = family history; AD = age at diagnosis.

The above table suggests that the diagnosis of PA is predominantly seen in females (6) as compared to males (1). The age at diagnosis seems to vary across different life spans for this population. Five out of seven of the PA sufferers are married and family history suggests a strong genetic link in developing the condition (6 out of 7). This table also shows that half of the sample revealed being diagnosed with other conditions besides PA.

As a result of the analytic process, data interpretation originated five major themes. These were transitions to the PA diagnosis, PA beliefs, B₁₂ therapy, symptom experience and management and finally the impact of PA on individuals' lives. These themes mirror individuals' understandings of living with pernicious anaemia and are discussed below (Fig.4.4.1).

Figure 4.4.1. Thematic map showing five main themes regarding the illness experience of PA sufferers

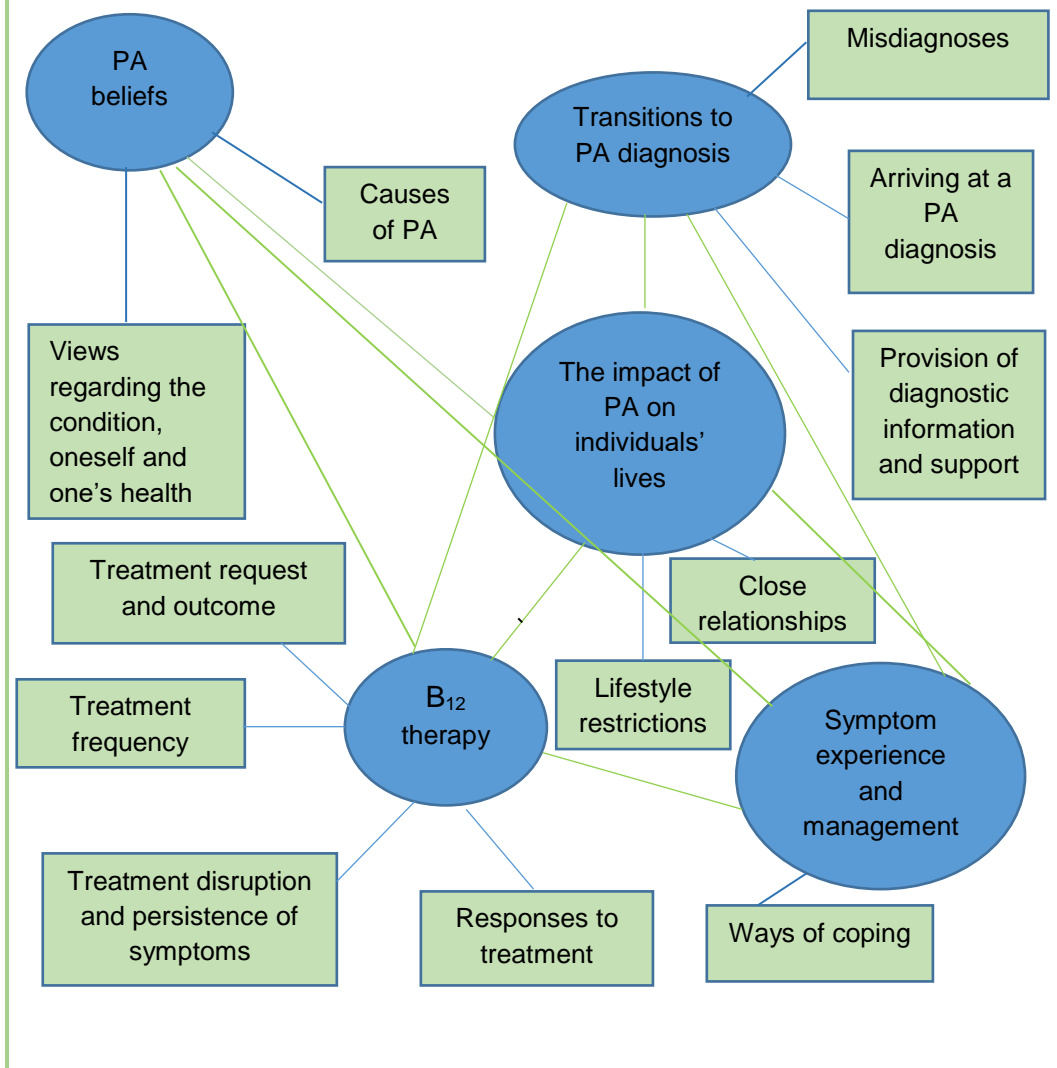


Figure 4.4.1. Themes reflecting the experience of PA sufferers.

4.5 Transitions to PA diagnosis

The superordinate theme of transitions to PA diagnosis considers the experience of being misdiagnosed prior to reaching an accurate diagnosis that would explain the experience of symptoms. The extent to which adequate information and support were provided at the time of diagnosis, as well as to what extent seeking online information was crucial towards the understanding of PA, is also discussed here.

4.5.1 Misdiagnoses

Individuals expressed their sense of frustration in not having an answer for their complaints. In this way, misdiagnosis seemed to reflect a traumatic event in individuals' lives.

"...I knew something was not right... so I went to the doctor which said, 'you are getting older'." (Female, 49)

"...it was quite traumatic to begin with because I didn't know what was wrong with me..." (Male, 55)

"...I didn't feel I was being diagnosed properly. I felt very helpless and isolated (Female, 58)

While some individuals were initially given more than one misdiagnosis, depression seemed to be one of the most common misdiagnoses in this population. Nevertheless, individuals conveyed not really accepting the diagnosis of depression.

“...the first diagnosis, they thought it was Sleep Apnoea because I was sleeping for a long time. ...then my GP on my first visit decided that I was depressed and prescribed me with anti-depressants...they have mentioned myalgic encephalomyelitis if they didn't find anything”. (Female, 38)

“...I went back to see my GP the one that was good at the beginning and she said we had to investigate whether it was depression.”(Female, 21)

As a result of misdiagnosis, prescribed medication didn't seem to be of any help. On the contrary, in some cases it appeared to add up to the existing fear and uncertainty. While one individual decided to discontinue taking prescribed antidepressants, another individual felt not being taken seriously.

“....nobody understood what was happening... started treating me for a nervous breakdown, put me on antidepressants which were terrifying” (Female, 49).

“I didn't have the idea of where I was or what was happening... I didn't want any more tablets...” (Female, 56)

“I have been treated for almost two and a half years with anti-depressants which obviously didn't work, so I didn't know what was wrong with me” (Female, 38)

“They did keep me on it but I stopped taking them... because they didn't work” (Female, 25)

“...well, I didn't feel I was depressed... ... they have doubled my anti-depressants (Female, 58)

4.5.2 Arriving at a PA diagnosis

Individuals considered different ways in which health professionals reached their PA diagnoses. Individual accounts suggested that tests carried out to diagnose PA mainly included blood tests. However, some seemed unsure of what the testing entailed or the outcome of specific tests.

“After the blood test results, there appeared to be an imbalance in the red and white cells.” (Female, 25)

“I have had lots of blood tests .It came back that my intrinsic factor, I didn’t have it or something...” (Female, 49)

“I had the blood tests not the absorption test, so they decided they would give me a course of injections” (Female, 38)

“I took a blood test that was the first thing that was done, bone marrow test (Female, 56)

Individuals also mentioned that doctors expected the presentation of symptoms to reflect the observed levels of serum B₁₂.

“... B₁₂ was a bit low, the second blood test results came back at 80 [<200pg/ml] which was the level that the GP was expecting (Female, 49)

“...the doctor expected my B₁₂ to be lowest given the amount of symptoms that I was displaying” (Female, 38)

“They kept checking my B₁₂ and I just kept going straight down” (Female, 56)

Whilst some of the diagnoses were known by chance, other diagnoses were established because of suspected heredity and through further testing, motivated by the presentation of persistent symptomatology, in some cases.

"I was diagnosed by accident since my GP found a case similar to mine" (Female, 25)

"It was an accidental diagnosis rather than a proper one and it worries me that it could have been missed and I would have carried on the way that I have been feeling and it is such an awful thought" (Male, 55)

"...it was a straight diagnosis...my mum already suspected it" (Female, 21)

"Took about 3 months and it was by chance ...My sister had been checked and explained how I was and told her to tell me to get checked" (Female, 49)

"Symptoms persisted... they doubled my medication on antidepressants... I was still tired, dizzy...so they searched for another possible cause" (Female, 56)

"...it's really bad that I can't remember... I think that it could have been just a routine check for hormone replacement therapy..." (Female, 58)

At last, reaching a diagnosis provided a sense of positivity and reassurance that complaints were finally acknowledged.

"...having it diagnosed and confirmed was in some sense a relief." (Female, 25)

"...since the PA diagnosis I feel much more positive, the relief of knowing that something was wrong with me." (Female, 38)

"...the absolute key turning point in my life [having a diagnosis]..." (Female, 56)

4.5.3 Provision of diagnostic information and support

At the time of diagnosis, individuals' didn't feel they received enough information from their clinicians. While some individuals suggested that basic information was provided and that they didn't question the information, others felt the need to seek for further support. One individual conveyed getting information from a specialty clinician.

"No real information that I have been given after diagnosis" (Female, 25)

"They explained what B₁₂ deficiency was and that you have injections... as far as it goes..." (Female, 21)

"He gave me a printout off the internet, you know they do, telling me about that so I read that and I have learnt from that" (Female, 38)

"No [information], I went to see a private consultant and he just didn't say a lot" (Male, 55)

"I just went along with what the doctors said" (Female, 56)

"In fact I had more information of a nutritionist than from anywhere else" (Female, 38)

However, the ability to discuss PA related issues didn't seem to be encouraged by some health professionals in comparison to others.

"... Well, it is not encouraged by the GP. I think that they just think that you have got the condition, you have the injections and there is no more to discuss; up until now and after the diagnosis I have had little or no discussion on my condition, that can't be right, can it?" (Female, 25)

"I don't really... in my surgery not something you wish to discuss... the myth that they don't understand why people still feel the symptoms" (Male, 55)

"There are two doctors...one I wouldn't really talk to because he is rubbish...the other, he is quite happy to listen" (Female, 21)

"I feel that I can discuss it with my doctor if I wanted..." (Female, 49)

In general, short consultation times, less monitoring and lack of awareness and understanding seemed to be the main reasons suggested for the perceived ill support provided by health-care services.

"But how many minutes to we get? It wasn't really the lack of information but the lack of people listening" (Female, 38)

"...the medical profession should be able to give some kind of feedback and review patients on a regular basis" (Male, 55)

"I don't know why it hasn't been picked up earlier and don't know whether or not doctors will expect to see it" (Female, 56)

"They were nice but not particularly helpful, I felt that they wanted me to be depressed because that was the easy answer and they could prescribe me with medication" (Female, 38)

"I would hate to think that there are other people going through the same sense of helplessness for the sake of blood tests" (Female, 58)

As a result, some individuals searched for online information and considered accessing support groups to help them deal with their condition. This was helpful for some as it provided reassurance; however, it also made them feel less confident in their ability to cope, due to the perceived off-putting information that was presented online, focused on the negative illness experience.

*"I kind of looked into it more myself... on websites and on the PA society"
(Female, 25)*

*"It was a real sense of relief because I have found the information pages"
(Female, 38)*

"It is nice to see that my symptoms are on the list" (Female, 56)

"I felt reassured that the symptoms that were described were similar to mine, but whether they were too spread out, I don't know" (Female, 49)

"A lot of what you read is very negative... makes you feel like you will never be able to achieve certain things" (Male, 55)

Others felt that they were already dealing with their condition and therefore did not feel that asking for support at the current time, would potentially be of benefit to them.

"I have joined [the PA Society] but I don't engage with them... I wanted to access the information... but found a bit whingey for my liking..." (Female, 25)

"No... I would give it a go... but I don't think so" (Male, 55)

"No, probably at the beginning I would have found that quite helpful... for 7 years I have been left to cope with this. I would see as a step backwards..." (Female, 49)

"Absolutely not, I am gullible about it, and there is no information anywhere" (Female, 58)

Whilst managing a complex condition, support provided by the immediate family and friends seemed to be valuable. However, one individual reported concealing the illness from other individuals.

"Definitely, I think that is really necessary [support]" (Male, 55)

"My friends and family support me; they completely accept it [my condition]... in work as well" (Female, 38)

"S [my daughter] she took over when I was unable. My husband has the patience... I think it must have been very hard for him..." (Female, 49)

"Yes, my mum, she is good and we talk about it and stuff" (Female, 21)

"Lots of people don't even know... my wider family knows, they probably don't give a second thought, my close family would" (Female, 58)

Brief summary discussion of the superordinate theme ‘transitions to PA diagnosis’

It may be reasonable to suggest that B₁₂ deficiency might not be on the health professionals’ radar (Hooper, 2014). Further, chances of a delayed diagnosis may also be increased, as available testing is not reliable (Devalia, Hamilton & Molloy, 2014). These results support a survey study with members of the PA society (N=889) suggesting lack of testing at time of diagnosis (for one-third of respondents) and delays between experiencing symptoms and getting a diagnosis (10 years for one-third of respondents), (Hooper, Hudson, Porter & McCaddon, 2014). Previous literature has suggested an increased prevalence of depression misdiagnoses in individuals presenting with chronic conditions (Boing et al., 2011; Moussavi et al., 2007). The nature of symptoms presented in PA such as negative affect, irritability, fatigue and sleeping disturbances may overlap with other conditions such as depression (Boswick & Rackley, 2012). Misdiagnosis occurrences have also been documented for various chronic conditions such as chronic fatigue syndrome (Griffith & Zarrouf, 2008), multiple sclerosis (Chwastiak & Ehde, 2007) and type 2 diabetes (Parry, Peel, Douglas & Lawton, 2004). The outcomes from a study looking at the transition from the experience of initial symptoms to a diagnosis of gout in 43 British patients are closely related to the findings of the present study (Liddle et al., 2015). It was suggested that diagnostic delays resulted in misdiagnosis and the difficulty in arranging timely consultations. However, unlike PA sufferers, other reasons for diagnostic delays related to delays in seeking medical advice due to financial pressures and self-diagnosis/treatment.

Patients were also not very accepting of their gout diagnosis, due to misconceptions attached to the condition (e.g. lifestyle, stigma), (Liddle et al., 2015).

A CFS study by Dickson, Knussen & Flowers (2007) also reported findings of delayed diagnoses and dismissive experiences, which added strain to doctor-patient relationships when patients contested their misdiagnosis. Doctors seemed to have encouraged adherence to anti-depressants. However, patients decided to discontinue the anti-depressants. CFS patients felt reassurance once the diagnosis was confirmed and suggested being active agents in managing their condition as they changed doctors and sought for the validation and support that they needed (Swoboda, 2008; Dickson, Knussen & Flowers, 2007). Similar to PA sufferers, both gout and chronic fatigue syndrome patients expressed the desire for more information and support at the time of diagnosis as patients were not aware of limitations in diagnostic testing for both conditions, or that gout reflected a condition with a chronic course. Taking action after receiving the diagnosis was a predominant theme. Patients asked for referrals, searched for further information and joined discussion groups to help them manage their condition. A qualitative study exploring the diagnosis of type 2 diabetes in 40 newly diagnosed patients emphasizes the relief of accomplishing a diagnosis and the crucial need for information and management advice (Parry, Peel, Douglas & Lawton, 2004).

Support from family and friends has been previously reported as providing a safety net for promoting self-esteem (Miller & DiMatteo, 2013; Falk, Wahn & Lidell, 2007), however this is not always the case.

Studies have also reported loss of friendships and individuals' feeling isolated due to their family and friends not being able to understand what they were going through (Dejean, Giacomini, Vanstone & Brundisini, 2013; Dickson, Knussen & Flowers, 2007).

4.6. PA beliefs

This theme incorporates individuals' beliefs regarding the causes of PA and views regarding the condition, oneself and one's overall health.

4.6.1 Causes of PA

Individuals expressed their understanding regarding what could be the possible causes of PA. These mainly incorporated genetic and nutrition related causes. Biochemical changes, stress, viral illness and nutritional deficiency were also perceived as potential causes of PA. However, genetics emerged as the most common perceived cause for developing the condition.

*"... I suppose there is an imbalance between the cells inside your system."
(Female, 21)*

*"I had a very bad gastroenteritis, I don't know but I have read that PA may be misdiagnosed as IBS, I do wonder if there was something that was triggered or whether or not you fit things that may not have a connection but because it is convenient. Whether I can say that was definitely the cause I can't say that ...there was a lot of stress leading up to this so whether that was a factor I don't know."
(Female, 38)*

*"... just the vitamin in my blood... don't know if I would say it is a genetic thing"
(Female, 58)*

"Well, genetic because there is a strong link in the family" (Female, 49)

"I don't know if it was anything... when my mother said, I have got that, I thought, well it has been passed through her, so I did think that" (Female, 56)

"I have been told it is hereditary as my brother and father had it." (Male, 55)

4.6.2 Views regarding the condition, oneself and one's overall health

One individual has mentioned the importance of not perceiving her condition as a disability, whilst another appeared to be aware that she had changed as a person.

"My supervisor wanted me to put it down as a medical illness in case I couldn't fulfil work... no... I don't class it as a disability" (Female, 38)

"...it does affect you, it has changed me... I am not as spontaneous as I would be before. I had bags of energy" (Female, 49)

Whilst no major problems were mentioned regarding one's overall health, one of the participants affirmed worry of developing a serious illness. In addition, one participant has stated that although she perceived herself as being sick, it did not seem to have an impact on her overall health.

"My health is good" (Male, 55)

"I am pretty fit and well... the only thing is that I have read that there is an increased risk for stomach cancer... a bit of a worry" (Female, 25)

"I don't have any other major problems" (Female, 21)

"I am quite a sickly person... but there is nothing majorly wrong with me...I feel healthy I think". (Female, 38)

Brief summary discussion of the superordinate theme 'PA beliefs'

Individuals often make causal attributions when trying to make sense of their condition (Grayson et al., 2014; Hoth et al, 2011). Individual interpretations of the causes of PA are mainly supported by the literature, suggesting a strong link with genetics (Banka, Ryan, Thomson & Newman, 2011; Conrad, 2009). Research has suggested that gout patients attributed 'infection' and 'working too much' as causes for symptoms experienced (Liddle et al., 2015), while patients with systemic vasculitis mentioned 'stress' and 'immunity' as the main causes for their condition (Grayson et al., 2014). It is not uncommon for individuals to perceive challenges to their personal identities as a result of being diagnosed with a chronic condition such as multiple sclerosis, asthma or diabetes (Bell, Tyrrell & Phoenix, 2016; Voltzenlogel et al., 2016; Cheek & Oster, 2002).

Narratives of patients living with CFS also highlight perceived changes in self-awareness because of the stigma attached to the condition (Tucker, 2008). This is also reflected in two accounts of PA sufferers, in terms of their perception of having PA. Individuals living with chronic conditions seem to overall perceive a poor health status (Barreto & Figueiredo, 2009; Machón, Vergara, Dorronsoro, Vrotsou & Larrañaga, 2015), however the opposite may also be true (Megari, 2013).

PA sufferers in the currently study did not seem to feel that their overall health was compromised by their diagnosis, even though they expressed worry about their prognosis. The likelihood of developing gastric carcinoids as a consequence of PA has been previously reported in the literature and may relate to a legitimate fear experienced by PA sufferers (Kokkola et al., 1998).

Fears concerning illness progression have also been reported by individuals suffering from various conditions such as diabetes, chronic fatigue syndrome and arthritis (Papaspurou et al., 2015; Berenbaum et al., 2014; Clements, Sharpe, Simkin, Borrill & Hawton, 1997).

4.7 B₁₂ therapy

B₁₂ therapy represents an overarching theme in the present study. This theme includes the sub-themes of treatment frequency, response to treatment, disruption of treatment and symptom persistence, and request of treatment and its outcome.

4.7.1 Treatment frequency

The frequency of treatment seemed to vary between 6 weeks to 3 months. One individual mentioned that blood tests were monitored concurrently with her scheduled injections. However, one individual confirmed only receiving initial B₁₂ treatment (loading doses) and another individual seemed to still be waiting to receive initial B₁₂ treatment.

“...I go every 3 months” (Female, 25)

“...only for the 3 monthly injections” (Male, 55)

“ A bit robotic, you go every three months, they give you the jab and check bloods every six weeks to 2 months” (Female, 49)

“I had the 6 injections in a short period of time” (Female, 58)

"I haven't been back to see her since... I will go back before my loading doses"
(Female, 38)

4.7.2 Response to B₁₂ therapy

Most individuals seemed to have perceived a considerable improvement in symptoms as a result of treatment. Receiving B₁₂ therapy was conveyed as a joyful experience for one individual.

"I think I was the happiest person in the world to have the PA injections, it got to a stage that I thought that I was going mad, I could feel that something was wrong with me." (Female, 49)

"Feel better 2/3 weeks after the injections... full of energy not just a foggy brain" (Female, 25)

"Before it was a complete stop of your body really. It works for me... feel much better" (Female, 38)

"You could see a noticeable difference" (Male, 55)

"Having the injections have made me feel better. I have the injection and definitely have got more energy" (Female, 56)

However, mixed perceptions regarding the benefits of B₁₂ therapy were also manifested. Whilst receiving treatment seemed to work for one person, another person questioned her perception of symptom improvement.

"...as long as I get my jabs, won't make a difference" (Female, 21)

"I think I have seen the difference but as I say I don't know how much of that is physical or psychological" (Female, 49)

4.7.3 Treatment disruption and persistence of symptoms

Whilst receiving treatment resulted in the improvement of symptoms for the majority, it was also revealed that for a few individuals, treatment disruption resulted in symptom relapse. Two individuals revealed missing scheduled treatment and one individual said that her clinician initiated treatment disruption, reflecting inconsistencies in the management of the condition.

I have missed injections... meaning that had injections late and that made me feel really bad, tiredness, toes and feet numb... dizziness" (Female, 25)

"I have had a year without the injections and I have missed the timeline" (Female, 21)

"...it was the B₁₂ injection every three months and I did that for a couple of years and then the doctor said that my level was fine and that I didn't need it anymore. I have had a year without the injections, and my doctor said I should never have stopped having the injection, and I said I did not stop it, he did. After my injections were stopped for about a year, then I was being breathless all the time and I was tired and I went back to him and he did a blood test and that was the problem, it was really low and I needed the B₁₂" (Female, 58)

4.7.4. Treatment request and outcome

Participants felt the need to ask for more frequent injections due to perceiving decline in symptoms before their next scheduled treatment. Whilst requesting early treatment appeared to be optional for one individual, it did not seem to be the case for the other individuals.

"I have discussed to see if I could go a week over because I am feeling a lot better" (Female, 49)

"I have asked for more frequent injections in the past... times when I need more energy... feel I need every 2/2.5 months. I have asked for 3 times... they are not willing to give me... because you may become dependent... they think it is psychological. My B₁₂ levels are so high... It is not nice... my feet and toes go numb... doesn't make you feel very nice... I just get on with it. If I had a choice I would have more frequent injections" (Female, 25)

"No I haven't requested it, I was kind of dictated" (Male, 55)

"Changing the initial treatment... there is a fear... so I am assuming that they know what they do" (Female, 38)

Brief summary discussion of the superordinate theme 'B₁₂ therapy'

There is mixed evidence regarding treatment satisfaction in chronic illness and this varies according the type of condition presented, individual responses to treatment and it may also be dependent on factors such as self-management (Spessotto et al.,2016; Clarke, Yates, Smith & Chico, 2016; Schulman-Green et al.,2012). One individual has mentioned not being able to acknowledge whether treatment resulted in the improvement of physical or psychological symptoms. This could possibly be related to one's illness identity. Further, misattributions of one's symptoms may negatively impact on the self-management of one's condition (Clarke, Yates, Smith & Chilcot, 2016; Liddle et al., 2015; Petrie & Weinman, 1997).

These accounts of PA sufferers are partly supported by findings in the PA survey (Hooper, Hudson, Porter & McCaddon, 2014). In this survey, members expressed dissatisfaction with their current treatment regimes and reported using a non-licensed form of B₁₂ to supplement their prescribed injections.

The need to request more frequent treatment may seem unusual when generally there is documented evidence of poor adherence to prescribed treatment in chronic illness (Chiolerio, Burnier & Santschi, 2016; Brown & Bussell, 2011; Rose, Comino & Zwar, 2005). However, literature has previously documented frustration with treatment in other conditions that are complex in nature such as chronic fatigue syndrome (Ax, Gregg and Jones, 1997) and rheumatoid arthritis (Barton, 2009), where tailored treatment is crucial.

4.8 Symptom experience and management

This theme encompasses the types of symptoms perceived by individuals as well as ways in which they have attempted to deal with these. Individuals appear to have experienced similar symptoms with varying degrees of severity. These included general symptoms such as fatigue, symptoms involving the nervous system such as pins and needles, and symptoms of a psychological nature such as mood swings and concentration problems.

“Brain fogginess, memory lapses, tiredness, feeling that I could sleep all day, numb fingers and toes and a bit achy... before I was diagnosed I used to pass out a lot, pins and needles in my legs...”(Female, 25)

“Exhaustion and knock on effects of sleeping deprivation” (Male, 55)

“Really tired... very stressful... my arm aching” (Female, 21)

“Pins and needles, tiredness, falling asleep a lot, concentration, low energy, less tolerant and more irritable” (Female, 49)

“Extreme tiredness, sleepiness, headaches, nerve pains, weepiness, more sensitive, less concentration, mood swings” (Female, 56)

"Tired and lethargic and breathlessness, that's the biggest thing, I feel like that when my injections are due, about 2 weeks before" (Female, 58)

4.8.1 Ways of coping

Whilst some individuals felt they could manage their symptoms, others didn't feel able to control their symptoms. Ways of coping included lifestyle changes such as exercising and changing one's diet and/or giving in to symptoms.

"I don't, how do I manage it? I don't know, I never think about it" (Female, 56)

"I don't manage them; just make sure that I get the appointment in the diary" (Male, 55)

"Your body wouldn't obey you...before I would feel completely out of control because I didn't understand what was going on..." (Female, 49)

"When I eat certain things for a while I feel better...if I go to the gym I can do a lot more stuff in general" (Female, 25)

"I still go to the gym 4 times a week even if I am exhausted... I ignore them [symptoms]. I think it may be psychological, when you pay too much attention..." (Female, 58)

"I have changed my diet and transformation has been dramatic... exercise is brilliant...everything I have to plan" (Female, 38)

"I have to say that I pretty much have given into them [symptoms]... I have started recently to try and exercise" (Female, 21)

Brief summary discussion of the superordinate theme ‘symptom experience and management’

Symptoms resulting from PA have been reported elsewhere and these include general (e.g. extreme tiredness) neurological (e.g. pins and needles) psychological (e.g. mood swings) and gastrointestinal symptoms. However, some individuals found it difficult to deal with symptoms on a daily basis (Hooper, Hudson, Porter & McCaddon, 2014). Attempts to cope with symptoms vary from ignoring symptoms to engaging in meaning-focused coping (Cameron & Wally, 2014; Ax, Gregg & Jones, 2001). A study with chronic kidney disease patients has found that patients engaged in maladaptive coping such as holding on to feelings of anxiety and depression, as well using adaptive behaviours such as engaging with healthier lifestyles and physical activity (Clarke, Yates, Smith & Chilcot, 2016; Knowles et al., 2014). These types of coping strategies have been extensively reported in the literature (Ji et al., 2016; Englbrecht et al, 2012; Avşar & Kaşıkçı, 2010; Nater et al., 2006).

4.9 The impact of PA on individuals' lives

Mixed views regarding how PA affects one's life seem to be noticeable. However, accounts' regarding the impact PA poses on their lifestyle and close relationships give the impression of the burden in one's life.

4.9.1 Lifestyle Restrictions

Individuals seem to have the understanding that PA is limiting in different ways from affecting one's mood to preventing individuals' from fulfilling their social roles.

"Only if I don't have the supplement ...you have to remember to organise in order to get your supplement or you will deteriorate rapidly" (Female, 25)

"Times which is very hard to get up... feel quite irritable and I am exhausted" (Female, 56)

"Tired and stressed about stuff" (Female, 21)

"It inhibits your lifestyle because you have to be mindful of how you are going to feel "(Male, 55)

"You are so limited when having a bad time" (Female, 49)

"I found that in the past my social life disappeared" (Female, 38)

"Yes, it does sometimes, because when I am due for the injection I am more aware of myself and that I do probably less because I haven't got as much energy and because of the breathlessness. I am very careful when I am in work, we have got lots of stairs where we are, so I go up to the 4th floor quite often, so when it's getting to the end of the treatment you know I need it again and use the lift, so I do adapt..." (Female, 58)

Some individuals acknowledged that PA didn't seem to impact on their lifestyle, as they accepted the condition and since moved on.

"I don't think it impacts on my life that much... only my productivity may drop at work" (Female, 21)

"I guess I try to get on with it" (Female, 25)

"Yes, definitely not for the better, however I accept it maybe too easily, so that is what you have got, that's how I feel, so you just carry on" (Female, 58)

4.9.2 Close relationships

PA seems to affect close relationships. In one way, knowing that family and friends are aware of the condition seems to ease the pressure placed on individuals'; however, mood changes have also been suggested to impact on one's family to a greater extent.

"My friends are aware of it now so they know that they need to give me warning of what is going on. It has caused difficulties but I think that they could see how unhappy I was" (Female, 38)

"I think that the only person noticing is my partner... it might be a bit lonely for him" (Female, 49)

"It has been hard on the family"... and still does to a certain extent" (Female, 58)

"It will cause difficulties for those close to me in terms of becoming more irritable" (Male, 55)

Brief summary discussion of the superordinate theme ‘the impact of PA on individuals’ lives’

PA seems to create a burden to individuals by impacting on different areas of their lives and consequently affecting adjustment to their condition (Hooper, Hudson, Porter & McCaddon, 2014). Accounts of strained relationships and disruptions on one’s social structure have been previously reported in the literature (Golics, Basra, Finlay & Salek, 2013; Wittenberg, Saada & Prosser, 2013). Alternatively, illness acceptance and have been found to facilitate the adaptation to one’s illness (Kostova, Caiata-Zufferey & Schulz, 2014; Pierobon, Giardini, Callegari & Majani, 2011).

4.10 General discussion

The present study sought to investigate individuals' experiences of living with a chronic condition such as PA. The superordinate themes that surfaced from this study related to transitions to PA diagnosis, PA beliefs, B₁₂ therapy and symptom experience and management. Each of these individual themes contributed to the impact of this condition on individuals' daily lives, mainly resulting in lifestyle restrictions and affecting close relationships. The process implicated in achieving a PA diagnosis reflected patients' perceived need of validating and improving the severity of symptoms experienced. However, these decisions were dependent of clinicians' judgements, inaccurate in most cases. Progressions to diagnosis involved the experience of misdiagnosis for the majority of individuals. Emotional trauma, feelings of uncertainty and isolation characterised responses to the dismissive attitudes of GP's (Duck et al., 2014). A reasonable shift in these responses was identified once a diagnosis of PA was achieved and B₁₂ therapy initiated, as individuals expressed more positivity and energy. However, for some individuals, current treatment practices didn't seem to be effective in the management of individual symptoms. Perceptions of symptom relapse and dissatisfaction with these practices that did not take into account individual variations in symptoms, seemed to have influenced the way individuals' coped with their illness experience, subsequently impacting on symptoms and psychological adjustment. The link between these superordinate themes highlights the influence of illness identity and locus of control as factors that are associated with the development of specific coping styles that may be adaptive or maladaptive in nature, affecting health outcomes.

Perceptions of low illness control may also be related to the perceived suboptimal management of PA (Joseph, Neeraj & William, 2014; Klok, Brand & Moss-Morris, 2010). Perceptions of illness control have been previously suggested to predict illness adjustment through behavioural responses such as cognitive reappraisal and seeking social support (Wiley, Cleary, Karan & Stanton, 2016; Diefenbach & Leventhal, 1996). Alternatively, engaging with denial and avoidance have been suggested to have a detrimental effect on illness adjustment (Kaptein, Klok, Moss-Morris & Brand, 2010; Hagger & Orbell, 2003). The findings of the current study have significant clinical implications in terms of guiding the development of psychosocial interventions aimed at improving perceptions of control and coping responses in PA sufferers.

The current study draws attention to the difficulty of managing a chronic condition such as PA, where symptoms may be varied and non-specific (Devalia, Hamilton & Molloy, 2014). The attribution of symptoms to psychosomatic causes have contributed to the delegitimization of the illness and challenged one's sense of identity (Åsbring & Närvänen, 2002; Ware, 1992; Strauss & Corbin, 1990; Charmaz, 1983).

Nevertheless, whilst GP's may not initially identify pernicious anaemia, misdiagnosis ought not to be a justification for not further seeking a differential diagnosis and not listening to patients' complaints (Otto, 2017; Carmel, 2008). Individuals' scepticism regarding clinicians' PA knowledge seemed to have affected the doctor-patient encounter and consequently, the management of the condition. However, to a lesser extent, confidence in the management of PA, illness acceptance and provision of valuable support have also been reflected in individuals' accounts.

The current study findings are partly supported by a survey investigating issues with diagnosis and treatment with this population (Hooper, Hudson, Porter & McCaddon, 2014). The findings of the current study mainly fit with existing chronic illness research, supporting the notion of the impact of a diagnosis and its effect on the individual as a whole (Spessoto et al., 2016; Cameron & Wally, 2014; Liddle et al., 2015; Grayson et al., 2014; Dejean, Giacomini, Vanstone & Brundisini, 2013; Golics, Basra, Finlay & Salek, 2013; Megari, 2013; Boswick & Rackley, 2012).

This study has contributed to the understanding of the psychosocial factors implicated in PA and highlighted the need to improve patient experiences of a PA diagnosis. However, as a small-scale qualitative study, findings may not be generalizable. Nevertheless, this study presented information with appropriate depth and contextually representative of the purposive sample (Burmeister & Aitken, 2012), allowing replication of the current study (O'Reilly & Parker, 2012). While thematic analysis is an appropriate method to analyse the perceptions of living with PA, being driven by the research question, its interpretive power may also be challenged. For example, it would be possible to infer on the use of language if another method such as discourse analysis was used (Poland, 2002). Previous studies have highlighted the power of linguistics in inviting or rejecting the patient into the process of diagnosis (Undeland & Malterud, 2008; Fleischman, 1999). Further, the interpretation of themes would have been more reliable if feedback was requested from participants as part of the analytic process (Anderson, 2010).

This study included participants from one ethnic group. While this is important regarding the primary endpoint of this thesis, which is to develop a screening tool that will be validated for the British population. It would also be useful to explore the experiences of patients from diverse ethnic backgrounds to investigate the role of cultural factors in defining one's experience of a PA diagnosis (Davidson et al., 2007). Another potential limitation could relate to the retrospective nature of individuals' accounts. However, this may also represent a potential strength as the sample included individuals' that were at different stages of their PA diagnosis. Respondent bias could have potentially influenced the results, however this may be inherent to the research process (Bowling, 2005).

Conducting focus groups to explore routes to diagnosis and treatment of PA would also be helpful to gain an insight on the challenges faced by health professionals. This way, both patients and clinicians' perspectives would be considered.

There is still the need to further study psychosocial factors to a larger extent in this population. Therefore, this study will serve as basis to develop study 3, an online survey aimed to further explore topics that emerged from the current findings, such as treatment supplementation, coping, identity, the impact of PA on one's quality of life and the provision of support, through the perspective of the members of the PA society, by using a mix-methods approach (Bishop, 2015).

Individual perceptions are key determinants on the way individuals' manage their illness, directly impacting on one's emotions and response to treatment. However, investigating these is not usually sought by health professionals.

The current study is the first to effectively address individuals' perceptions of their PA experience. The qualitative nature of this study has further developed the understanding regarding the pathway from diagnosis through treatment and management of this condition, taking this research a step closer to its overall aim. This has implications for clinical care in terms of considering effective practices that would provide tailored care, considering the individual variability in the response to B₁₂ therapy. These practices ought to consider a holistic approach which would be valuable when treating and measuring outcomes in PA. Greater recognition of this condition would also strengthen the patient-doctor relationship, and potentially reduce the burden of disease at primary and secondary levels.

4.11 Reflexive analysis

Patients' perspectives are crucial in the development of effective approaches to the management of chronic illness, and contribute to the overall aim of the current thesis. In the current study, I have conducted semi-structured interviews with individuals suffering with pernicious anaemia. There was a great contrast concerning data collection procedures in study 1 and the qualitative nature of the current study. The experience of conducting face-to-face interviews as opposed to collecting patient recorded data was stimulating as I was able to further clarify any issues arising from the research and add more meaning to the data. This study has strengthened and developed my current knowledge of PA.

I felt that individuals were comfortable in the environment where the interviews took place. This most included their homes (as per choice) which may have provided a sense of security and control (Ecker, 2017). In this way, rapport was not difficult to achieve.

Whilst conducting interviews allowed individuals freedom in answering the questions, I acknowledge that my presence may have influenced this, in comparison to using other data collection methods, such as self-report questionnaires. I have probed individuals to express deep views to obtain rich data. Nevertheless, it may be argued that this is part of the research process, and potential bias is present despite the method of data collection selected.

Whilst there was an attempt to provide summaries of the understanding of individuals' accounts throughout the interviews to ensure no information was missed it is acknowledged that the validity of the data would have been strengthened if participants were asked for their feedback on the themes that emerged from the data analysis, as it would further ensure addressing interpretive inconsistencies by challenging researchers' assumptions. The interview transcripts were read by an additional experienced researcher to ensure data reliability.

The themes reflect meaningful issues beyond the topics that were raised. Examples refers to the lay understanding of the nature of individual symptoms and worry regarding the prognosis of PA.

It was evident from one individual account that participating in this research made the person consider their pattern of symptoms and acknowledge the perceived need to request earlier treatment. In this way, this study may have possibly elicited a cathartic experience.

I have felt an empathic understanding toward individuals' experiences, specifically regarding the lack of information and support in dealing with their condition. Even though I could not relate to the experience of living with a chronic condition, this might have helped reduce the subjectivity of the analysis. Nevertheless, it may also be argued the extent to which empathic understanding may have overemphasized individuals' powerlessness in dealing with their condition.

I am also aware that individuals' expectations of improved management were possible despite attempts to explain that the aim of the current research was to develop a further understanding of the condition.

Data generation and interpretive analysis support the theoretical framework in the current study and most importantly are true reflections of individuals' experiences.

Chapter 5

Study 3: A survey study of the PA experiences of members of the Pernicious Anaemia Society

5.1 Study Aims

The present study aims to investigate the experience of PA, through the perspective of the PAS members'.

5.2 Background

The current standard of care in PA follows the "one-size fits all regimen" (Hooper, Porter & McCaddon, 2014). The perceived severity of patients' symptoms, the inability to control these and the constant fight to get adequate treatment results in increased psychological distress. This drives maladaptive illness responses and directly impacts on health-related quality of life.

This poses profound implications for PA patients, resulting in lifestyle restrictions such as the inability to fulfil social roles that may influence individual's illness beliefs and sense of control, inhibiting coping, and affecting quality of life. Many individuals turn to patient organisations and/or forums for support to help them deal with their condition. Much of this support is provided online.

Existing literature has documented the beneficial impact of support groups in facilitating illness adjustment therefore enhancing quality of life (Beacham, Linfield, Kinman & Payne-Murphy, 2015; Sherman et al., 2008; Coppa & Boyle, 2003). For example, the vitamin B₁₂ deficiency charity support group (B₁₂d) assists people who are B₁₂ deficient due to various causes. Patient organisations such as the Pernicious Anaemia society (PAS, 2008) strive to empower individuals and help reduce the stigma of being diagnosed with PA.

The PAS is an international charity, based in the Bridgend area that provides information and support for individuals diagnosed with PA as well as their families. The PAS was founded in 2005 by the current Executive Chairman, Martyn Hooper and in 2006 was part of the U.K's charity commission. The members of the PAS contribute to its sustainable funding which was introduced in 2009. The PAS is run by volunteers and includes eight trustees across the UK and currently, it includes more than 7000 members. The PAS has developed nine sub-groups (Gloucester, Isle of Man, South Wales, Los Angeles, Berkshire, Anglesey and North Wales, Missouri, Worcestershire and Wiltshire). The support provided by the PAS consists of leaflet information which outlines a description of the condition and problems that newly diagnosed individuals are likely to face; local support groups to minimise the social problems encountered, such as isolation, and a helpline which also provides a 'call back service'.

The PAS endeavours to raise awareness of the problems with diagnosis and treatment, by engaging with scientific research and making contact with relevant bodies to ensure that the management of PA is improved (PAS, 2008).

One of the most common complaints of the members of the PA society refers to PA treatment. Whilst replacement therapy may significantly improve symptoms, many patients remain symptomatic, perceiving the need for more frequent treatment. This represents a challenge for both individuals and clinicians. In many cases, individuals tend to resort to private treatment and/or self-treat to relieve their symptoms. Not receiving treatment tailored to one's needs significantly affects one's life in every aspect, from experiencing relationship problems to the inability to fulfil social roles (Hooper, Hudson, Porter & MacCaddon, 2014).

A survey carried out by the PAS have suggested that approximately half of the respondents (N=900) reported having low levels of B₁₂, however, further investigations were not carried out. This survey also indicated that 44% of the patients were initially misdiagnosed, 22% waited for 2 years for a diagnosis, 19% waited for 5 years and 14% waited for 10 years or more. However, the occurrence of misdiagnosis may potentially relate to the experience of symptoms that may not be generally associated with PA. These include mood swings, irritability and confusion (PAS, 2012). These findings support preliminary research (studies 1 and 2) which emphasized misdiagnosis, lack of control, symptom severity, social support and the impact of PA on one's quality of life.

Considering the dearth of research in this area, and to ensure that the findings of preliminary studies (study 1 and 2) reflect the issues faced by PA sufferers in general, investigating PAS members' illness experiences would ensure that a wider audience is reached. It is unknown how many patients diagnosed with PA, benefit from the type of support provided by the PA society.

PAS affiliates may be more focused on their condition and therefore may feel more empowered to voice their concerns. In this way, it would be expected that these individuals hold different illness perceptions.

Research with this population group would potentially strengthen existing findings as well as highlight any further issues with the management of PA.

5.3 Methodology

5.3.1 Design

An exploratory survey design containing both quantitative and qualitative components aimed to investigate PAS experiences of diagnosis and treatment. The data was collected online via Survey Monkey and included closed and open-ended questions, eliciting detailed responses. Given the comprehensive accounts of members' experiences, thematic coding was carried out (Braun & Clarke, 2006; Joffe & Yardley, 2004).

5.3.2 Ethical considerations

Ethical approval was granted by the School of Psychology in the host institution (University of Glamorgan) in line with the BPS guidelines (2010). Consent was obtained from participants via Survey Monkey. Participant data was kept anonymous and confidential. Participants were informed of their right to withdraw from the research at any time. Data were stored according to the university guidelines in accordance with the British Psychological Society (2010).

5.3.3 Sample

The purposive sample consisted of 199 members of the PA society. This included 172 females and 26 males with ages ranging from 19-83 years old (Mean age=45.5 years old, SD=13.3). Family history was recorded for 35% of the cases (n=70).

5.3.4 Materials

An advert was placed on the PAS platform inviting members to participate in the survey study (Appendix 3.1). The survey instrument combined demographic and clinical information and included closed and open-ended questions. The survey development was driven by the expertise of the research team, informed by a comprehensive review of the PA literature as well as findings of study 1 and 2. Examples of questions included "do you feel that treatment is working? How?" and "how do you cope with your symptoms? Please explain". (Appendix 3.2).

5.3.5 Procedure

The researcher contacted the chair of the PAS to post the advert and grant permission for members to access the survey link. Once this was agreed, the study was advertised by the researcher, in the PAS members' forum. The survey took approximately 30 minutes to complete and it was available for approximately five months (August 2012-January 2013). Once the research-associated tasks were completed, the researcher provided the summary of the research findings to be posted in the PAS members' forum by the chair of the PAS.

5.4 Results

This sub-section includes the quantitative and qualitative components of the survey. These findings were integrated, where pertinent, to reflect how the qualitative component links with the quantitative component.

5.4.1 Descriptive analyses

Data recorded included respondents' demographic information and PA related data. Data were checked for normality prior to computing descriptive analyses.

5.4.1.1 Normal distribution

The Shapiro-Wilk test was computed as numerical means of assessing normality for the variables of 'age and gender' for this population. This test is generally employed in small sample sizes <50 (Field, 2009).

Table 5.4.1.1.

Normal distribution for the variables of age in gender

Variables	Observed values		
	Shapiro- Wilk (W)	Skewness	Kurtosis
Age	W = 0.985 (p=0.031)	- 0.14 (SE=0.17)	- 0.70 (SE = 0.34)
Gender	W = 0.430 (p= 0.000)	- 1.90 (SE=0.17)	- 0.81 (SE= 0.32)

Note. SE = standard error; p = significance value.

The table above shows that the observed distribution for the variable 'age' does not fit the normal distribution.

This may be explained by the age of diagnosis which points to a higher demographic, where the typical onset is over the age of 60 years old for both males and females (Hinds, Johnson, Webb & Graham, 2011).

The variable 'gender' is also non-normally distributed. The uneven distribution in gender in relation to the diagnosis of B₁₂ deficiency/PA, weighs towards females.

Therefore, the data deviates from the normal distribution in age and gender. Nevertheless, this sample is partly representative of the PA population, where a higher prevalence would occur in older individuals and females. There is mixed evidence regarding the predominance of a PA diagnosis in females. While some studies confirm this (Hooper, Hudson, Porter & McCaddon, 2014; Carmel, 1996; Wintrobe, 1981), others confirm this may not be the case (Lahner & Annibale, 2009; Zittoun, 2001).

5.4.1.2 Respondent demographics

The sample (N=199; 172 females, 26 males; Mean age =44.4 years old, SD=14.6) indicated that the majority of the population were British (57%), followed by American (7%), Dutch (6%) and Australian (5%). To a lesser extent, other nationalities recorded included Canadian (2%), Indian (0.9%) Belgian, Swedish (0.4%), Norwegian (0.4. %), Polish (0.4%), New Zealand (0.4%) and Italian (0.4%). There was no information regarding the ethnic background for 20.1% of the population. Main occupations included the areas of healthcare (13%), education (10%), administration (9%) and business/finance (8%). 10% of the individuals were retired, homemakers (4%) and unemployed (3%).

5.4.1.3 Clinical data

Diagnostic information was available for 166 of the respondents. The diagnosis of PA was recorded in 56% of the cases, B₁₂ deficiency in 9% of the cases and malabsorption for 1% of the cases. Approximately 4% of the population were still waiting for a diagnosis and for 29%, this information was missing. In individuals with the reported diagnoses of PA/B₁₂ deficiency (n=154), PA family history was recorded for 32% of the population. 65% reported not having a family history of PA and 3% were unsure. Individuals suggested that B₁₂ deficiency investigations mainly comprised of a complete blood count (63%), followed by serum B₁₂ investigations (32%) and the IFAB (18%). Time since diagnosis was recorded for 69% of the population and it varied between 2 months and 30 years, being the most common being 1 year (12%). It was also suggested that test monitoring was not carried out since diagnosis(16%). 75% of the respondents reported having other existing conditions as opposed to 25% who confirmed not having any other conditions than PA. The most common conditions included hypothyroidism (9%) and asthma (6%). 64% of the individuals reported associating their existing conditions with PA.

5.4.1.4 Qualitative analysis

A full thematic analysis was carried out as wide-ranging accounts of members' experiences were provided. The interpretation of the data corpus reflected six super ordinate themes, revolving around the overarching theme of 'the impact of PA on one's life'. Themes are outlined in the below figure (Fig.5.4.1.4)

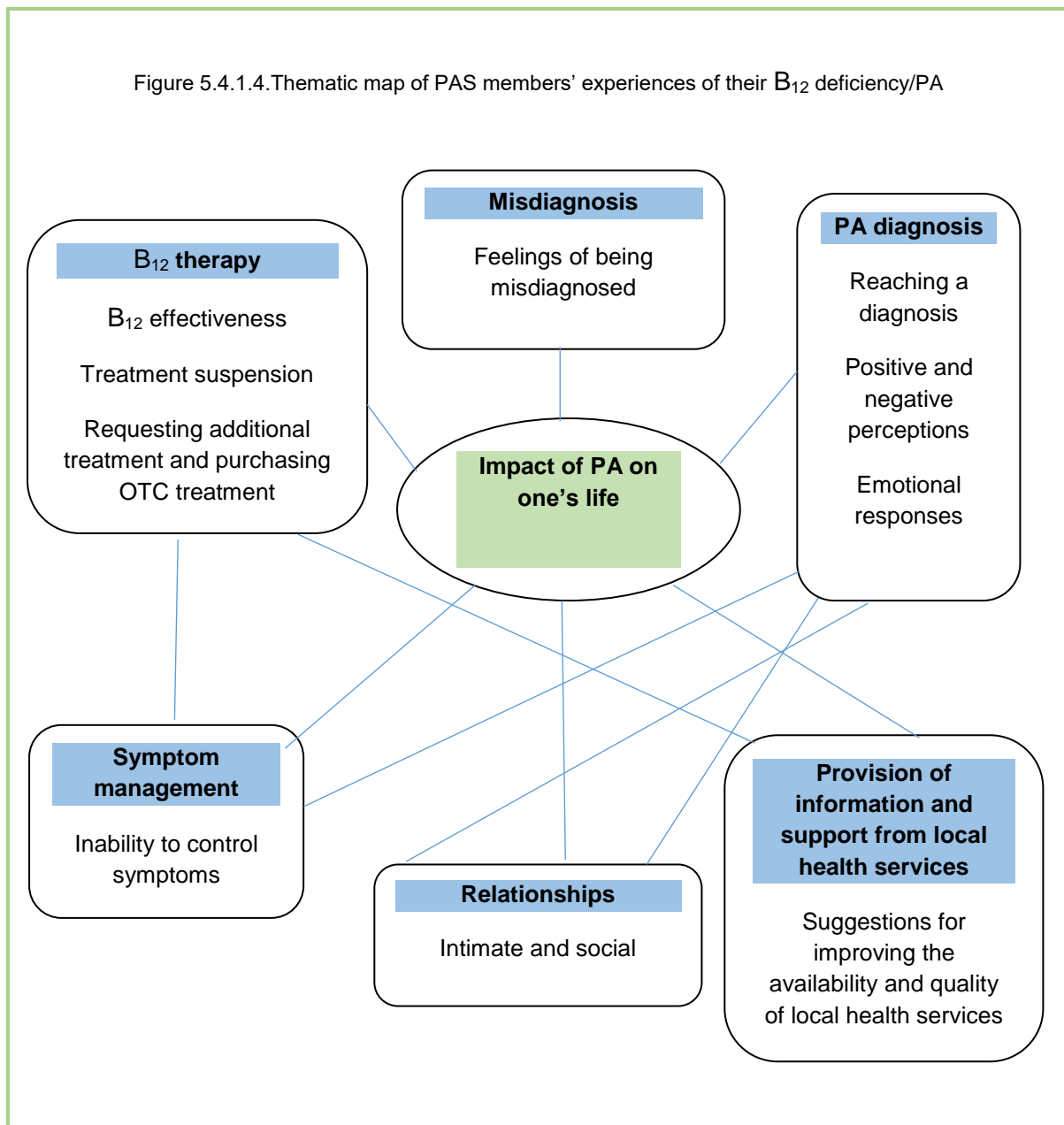


Figure 5.4.1.4. Themes that reflect the diagnostic and treatment experiences of PA sufferers.

5.5 Misdiagnosis

The theme of misdiagnosis has been quite prominent given the complex nature of PA. The majority of the respondents felt they were misdiagnosed, prior to receiving a PA diagnosis (65%), compared with 35% of the respondents, who didn't feel they were misdiagnosed. Misdiagnoses ranged from a viral infection to depression and irritable bowel syndrome. Further, diagnostic delays resulted in the exacerbation of symptoms leading to neurological damage. Nevertheless, some individuals had to deal with the uncertainty of a diagnosis.

"Anxiety, depression, chronic fatigue syndrome, IBS" (Female, 46)

"They told my mother I had leukaemia" (Female 29)

"Fatigue was considered to be related to psychogenic depression" (Male, 50)

"Irritable bowel, no diagnosis related to breathlessness and dizziness - just 'if it gets worse come back' type of thing..." (Female, 22)

"I have permanent nerve and neurological damage because of the delayed diagnoses" (Male, 37)

"I was just told I was an enigma" (Female, 60)

"As I am currently seeking a diagnosis again, I feel I have recently been misdiagnosed. My haematologist recently referred me to a sleep specialist as they have suggested I am tired due to sleep apnoea (despite no evidence of this). They have also suggested that I may be depressed and stressed which is why I am tired. They have also said my dizziness feeling/loss of balance is not a known symptom of B₁₂ deficiency and that maybe I should see a neurologist to see if there is something wrong in my brain" (Female, 31)

"I felt betrayed and talked to friends and family to find another doctor who finally made the diagnosis. I have permanent nerve and neurological damage because of the delayed diagnoses" (Female, 26)

"I went so long undiagnosed so symptoms and damage are extremely severe" (Male, 58)

"In some ways I feel I will never be truly well again due to being undiagnosed for so long. I feel the lack of B₁₂ caused irreparable damage" (Female, 72)

Given the non-specific nature of PA, it has been suggested that its symptoms may be masked to reflect in particular, other autoimmune conditions, making diagnosis difficult (Hooper, 2012; Banka, Ryan, Thomson & Newman, 2011; Pacholok & Stewart, 2011; Conrad, 2009; PAS, 2008; Stabler & Allen, 2004). PA sufferers may have a disposition towards developing other co-morbidities; however, studies undertaken have not been able to explain why this happens (Pacholok & Stewart, 2011; PAS, 2008; Alkhateeb et al, 2003). Co-morbidities such as depression (Kurlowicz et al, 1997; Onder et al., 2005; Fafouti, Paparrigopoulos, Liappas, Mantouvalos, Typaldou, Christodoulou, 2002), vitiligo (Alkhateeb et al, 2003), autoimmune thyroiditis (Zelisseen et al, 1995), multiple sclerosis (Miller, Korem, Almog, Galboiz, 2005) and diabetes (Tzellos, Tahmatzidis, Lallas, Apostolidou & Goulis, 2009) have been associated with PA. Research conducted by the PAS has reported that more than 50% of individuals have been diagnosed with another illness before being diagnosed with PA or B₁₂ deficiency (PAS, 2012).

Several studies have described patients suffering from severe neurologic manifestations for a long period of time because B₁₂ deficiency was not included in the differential diagnosis from their primary care physicians (Pacholok & Stewart,2011; Fragasso,Mannarella, Ciancio & Sacco, 2010;Matrana, Gauthier & Lafaye,2009;Paul & Reichard,2009;Turner & Talbot,2009; Kalita & Misra, 2008; Svenson,2007; Norman,2000).

Common neurologic complaints include weakness, paraesthesia, motor disturbances and various cognitive and behavioural changes such as dementia, depression and personality changes (Baik, 1999, as cited by Evatt et al., 2010; Savage & Lindebaum, 1995). Late diagnosis may significantly affect one's life, undermine the confidence in the medical profession and subsequently influence the doctor-patient relationship (Armstrong et al., 2017).

5.5.1 Feelings of being misdiagnosed prior to PA diagnosis

Throughout the process of misdiagnosis, individuals experienced feelings of hopelessness, fear, mistrust, frustration, disappointment, depression, anger, isolation and prejudice. While some accepted the diagnosis given at the time, others were determined to fight for a diagnosis that would match their symptoms.

"I gave up trying as doctors often made me feel like a fraud" (Male, 56)

"My partner thought I was dying of cancer I was too tired to care" (Female, 62)

"I thought I actually had cancer. I was preparing for the worst and I didn't believe I had any energy to fight it anymore"(Female, 53)

"Didn't trust the doctors too well, I reassessed my opinion of GPs." (Male, 61)

"I felt let down by the medical establishment "(Female, 31)

"Felt dismissed. Treated like a hypochondriac. Felt lost and demoralised but knew that it was not in my head. Had positive results ignored by specialists as it did not fit with what they were looking for MS, Lupus etc..." (Female, 41)

"I felt humiliated, ignored, not taken seriously and I am fed up of doctors only looking at the numbers of blood test results and not weighing up the relation of different results alongside symptoms. It is very hard to get an overview" (Male, 56)

"I feel very annoyed at previous GP surgery - I feel I have lost 3 years of my life – after the first course of injections I feel 10 years younger - but because of negligence I might have permanent nerve damage" (Female, 36)

"I nearly committed suicide, I was so sick and nobody cared. I was 16" (Female, 29)

"Are they having me on, is it because I am a woman, and a professional one at that, how come others get diagnosis and treatment? Do they think my symptoms are imaginary... 'hysterical', 'psychiatric'?" (Female, 53)

"I was frustrated as all the tests were normal yet I wasn't getting any better"(Male, 63)

"I was isolated and alone, with no future, no one listened to my symptoms." (Female, 24)

"I have pushed myself so no one could see how ill I was and how much I was breaking down inside" (Female, 52)

"Just accepted it. They were the experts as far as I knew" (Male, 42)

"I trusted the doctors to know what they were doing and just got on with it, for the next couple of years I learnt to live with my sore tongue and put it down to being run down or a bit stressed. The same applied to my sore joints I learnt to live with the pain" (Female, 79)

"I felt I was going to have to fight to get help, to demand some quality back in my life" (Female, 33)

"I knew something was being missed so I kept pressing" (Male, 58)

"I researched causes of symptoms and asked my doctor for more tests" (Male, 83)

"I have learnt to disagree, question, do my own research and ask for further tests or second opinions and I have paid for private blood tests and consultants to prove GPs wrong. The results from St Thomas's were a catalyst for better treatment as they realised that I knew more about B₁₂ than they did. It has been a very difficult fight" (Female, 41)

Studies have reported feelings that come with the emotional stress that individuals' experience when going through the process of misdiagnosis. These feelings include confusion, isolation, anger, frustration, fear, anxiety, disbelief, numbness, shock, worry and feeling overwhelmed (Duck et al., 2015; Armstrong et al., 2012; Conroy, 2004; Wilson & Fletcher, 2002). Other studies have reported depressive reactions (Jeon, Kraus, Jowsey & Glasgow, 2010; Floyd, 1997) long-term anxiety, emotional trauma and self-doubt (Barais et al., 2014; Kharrazi & Kharrazi, 2005). Illness perceptions in response to a diagnosis may be associated with different outcomes, which in turn change the overall illness experience (Wojcik, Armstrong & Kannan, 2011).

Research assessing illness experience, depression and anxiety with individuals with CFS has mentioned the beneficial role that legitimization of the illness has on improved psychological health. Individuals with CFS who stated that their GP failed to legitimize their illness reported more psychological distress as compared to their counterparts (Lehman, Lehman, Hemphill, Mandel & Cooper, 2002). Explanations of patients' common rejection of a psychiatric diagnosis are based on the interpretation of their symptoms being approached by doctors as mainly fictitious. Individuals experiencing chronic illness are often susceptible to psychosomatic interpretations of their symptoms, from healthcare professionals (Armstrong et al., 2017; Deale & Wessely, 2001).

Research investigating healthcare professionals' attitudes towards chronic illness patients' has reported psychological labelling as a source of distress for these individuals, aggravating the severity of their illness. However, there is also evidence to suggest that doctors may face interactional challenges when trying to ascertain symptoms that initially may appear unexplained (Monzoni, Duncan, Grünewald & Reuber, 2011; White 2001).

Delaying a diagnosis may result in the impairment of an individuals' health related quality of life (HRQoL). Reducing the diagnostic delay may significantly ease the burden of one's disease (Norstrom, Lindholm, Sandstrom & Ivarsson, 2011; Walters, Hansen, Walters & Wood- Baker, 2008).

5.6. PA diagnosis

The super-ordinate theme of PA diagnosis appears to be controversial since in most cases an early and straightforward diagnosis was not always reached. Reasons for this may include the lack of reliable testing and lack of awareness within health professionals to successfully diagnose PA. This theme encompasses the process of reaching a diagnosis, positive and negative perceptions of a B₁₂ deficiency/PA diagnosis and emotional responses resulting from the same.

5.6.1 Reaching a diagnosis

Individuals experienced different ways of achieving a PA diagnosis. In most cases, diagnosis was provided by their GP's following routine testing and/or patients' complaints of ongoing symptoms.

"Dr. took bloods for high blood pressure and noticed that I had very abnormal blood cells" (Male, 50)

"GP, after routine blood test" (Female, 22)

"I have repeated the tests three times until I got a positive result for PA" (Male, 60)

"I complained of tiredness, shortness of breath and cognitive problems. My GP ordered pathology tests which indicated PA, based on intrinsic factor antibodies and low serum B₁₂ levels" (Female, 36)

Family history seems to be a strong element to consider when reaching a diagnosis of PA. In addition, individuals' awareness/knowledge of their condition helped speed up the process of reaching a diagnosis.

"Known for almost 12 years something wasn't right related to B₁₂ absorption but doctors always would blow it off. I get B₁₂ shots from time to time... last week it barely improved, so I happened to Google anaemia and stumbled upon PA, never heard of it before. Texted my mom to ask if we had anaemia in the family... she replied that my Great Grandfather died from PA and both her/sister were treated for it too. This morning I already had an appointment to go over blood tests with the Dr. and I asked how my B₁₂ levels looked. She said they looked great, they are so high! I asked her if we could do a urine MMA test to check my B₁₂ and explained my family history and my symptoms that get blown off. She said because of your history and symptoms, we are going to start treatment today" (Female, 51)

"Went to give blood, they refused my blood, advised me to go to the doctor. He was testing for iron and I asked him to test PA as my mother was just diagnosed (in her 70s.). He was reluctant but did it. When results came he apologised and started me on injections" (Male, 46)

There are a range of existing routes to determine B₁₂ deficiency, however these may not be entirely accurate (Pacholok & Stuart, 2011; Devalia, 2006). A common form of diagnosis would refer to the search of typical haematological abnormalities and measurement of serum B₁₂. However, further investigations (e.g. MMA) and a therapeutic trial may be required (Devalia, Hamilton & Molloy, 2014; Savage & Lindenbaum, 1995). Nevertheless, it has been suggested that one of the issues with the diagnosis of PA may not be directly related to the nature of the tests performed but to an uncertain margin between B₁₂ depletion and disease (Carmel, 2003; Matchar, McCrory, Millington & Feussner, 1994 as cited by Evatt et al., 2010).

Some individuals also experienced an accidental diagnosis while being tested or treated for other co-morbidities.

"Diagnosed incidentally when visiting the Rheumatologist who was following me up for Polymyalgia Rheumatica" (Female, 51)

"I found out by accident by trying a B₁₂ skin patch as a remedy for the fatigue aspect in ME, the difference in me was rapid, substantial and almost unbelievable" (Female, 53)

"Diagnosed immediately following diagnosis of Hashimoto's Thyroiditis" (Male, 50)

"Originally saw the GP in 2006 complaining of tiredness. Blood tests revealed that B₁₂ was just below cut off point. GP told me I had post viral fatigue. In 2011, I saw a friend who is a doctor. I had Vitiligo and she advised me to get checked for heart murmurs etc. Looking up Vitiligo, I saw connection to PA and demanded a repeat blood test from my GP, subsequently diagnosed." (Female, 47)

PA sufferers are at increased risk of developing other autoimmune conditions such as thyroid disorders (up to 32%), rheumatoid arthritis, vitiligo, ME (Pacholok & Stuart, 2011; PAS, 2009; Alkhateeb, Fain, Thody, Bennett and Spritz, 2003; Zelissen, Bast & Croughs, 1995) and other conditions such as depression (Onder et al.,2005). Research has also reported the incidence of skin disorders (45%), tinnitus (40%), thyroid disorders (27%) and vitiligo (15%) as co-existing conditions among PA sufferers (PAS, 2012). However, studies undertaken have not been able to identify and/or establish a causal relationship between PA and other conditions (Onder et al, 2005; Alkhateeb et al., 2003).

5.6.2 Positive and negative perceptions of being diagnosed with PA

When asked about what has been positive and/or negative about the PA diagnosis, individuals' positive perceptions were associated to the relief of finally being taken seriously by health professionals, after a long struggle of trying to understand what was wrong with them. They also hoped that their symptoms would eventually get better.

"Finally being diagnosed has been a relief and I feel so much better and healthier as a result, having felt under par and struggling for years. Also frustrated it took so long to be diagnosed." (Female, 37)

"Relieved that there was a reason for my symptoms and I could begin to manage my condition" (Male, 30)

"The only positive was feeling I was not making things up and the initial booster injections made me feel a lot better" (Female, 26)

"The positive thing is that I have regained my self-confidence. I do no longer believe that I am a hypochondriac. I know that I correctly can separate between mental and physical sensations that can occur in my body, and I do not have more or stronger depressions/anxieties than most people, or pathological mental symptoms. I'm in hope for the future." (Female, 48)

Negative perceptions revolved around the idea of PA being a lifelong illness, the accompanying symptoms, complications that emerged as a result of a late diagnosis, being subject to labelling, the perceived lack of knowledge from health professionals, and awareness of not getting the adequate treatment for their condition.

"Negative is not getting enough treatment. My levels are still very low and I'm still very sick, but it's difficult to get more B₁₂ injections" (Female, 60)

"Very little awareness of PA and a perception that it isn't being taken seriously by the medical profession" (Male, 39)

"Negative - doctors' not understanding blood test results is absolutely bewildering" (Male, 57)

"Being labelled hypo, depressed, wished I was diagnosed years ago" (Female, 55)

"Negatives are feeling lousy for the majority of the time, falling asleep in the midst of doing things and the painful injections" (Female, 46)

5.6.3 Emotional responses

Individuals experienced a plethora of emotions when diagnosed with PA. These ranged from complete happiness to fear regarding the ability to manage PA in the future. For many, being diagnosed meant they could be released from the stigma associated to their 'unknown' symptoms and finally be accepted for their condition, therefore regaining their once lost sense of identity.

"I was delighted to have a diagnosis so I could tell people; it is not all in my head. I have actual proof and I can now start to get better and get back to the person I used to be." (Female, 48)

"It didn't come as a surprise considering my grandmother's history. I was concerned about prognosis, and how it would affect my life. As well as my training, as it affects the body's ability to break down amino acids and protein, and I was an athlete." (Female, 26)

"Shocked due to the fact that I had to research the condition myself to find out what was wrong with me and relieved it wasn't psychological like doctors had told me" (Male, 50)

"Shocked, upset and alone" (Female, 19)

"I am scared for what the future holds and for the unknown damage that has been done that could have been prevented if the proper checks were done 6 years ago. I have a history of type 2 diabetes and dementia in my family and believe I am now at a higher risk of getting these with having PA." (Female, 47)

"Relieved but angry that I had suffered needlessly for months" (Female, 60)

Despite these mixed emotions, the majority of individuals felt that PA was the right diagnosis. Physical and emotional changes started to happen through treatment, and for many it meant a new beginning.

"When the injections worked it felt right, despite controversy in the practice" (Female, 30)

"It all made sense. All my symptoms were exactly what PA is and I knew it was the right diagnosis" (Female, 58)

"On the whole I feel better - nearly all my symptoms have gone, and those that remain are mild and easy to cope with. It's not stopping me doing what I want anymore." (Female, 48)

"Physically I have improved dramatically but my highest improvement has been mentally and psychologically" (Female, 63)

"Suppression of anxiety and depression is a big relief" (Female, 37)

"I feel "normal" again and don't feel like I'm struggling to keep up. I used to think it was just me but I never knew why I didn't feel right, so I'm relieved and I feel I have a new lease of life." (Male, 50)

Studies have documented individuals' relief of getting a diagnosis of chronic illness. Similar to the statements of PA sufferers, patients reported feeling happy and relieved as they had a reason for their unexplained fatigue and could finally be freed from the label of being called a hypochondriac. Frustration was expressed regarding initial complaints not being further investigated by health professionals.

Feelings of uncertainty were also expressed regarding symptom improvement (Sexton & Loflin 2009; Ueland & Malterud, 2007). Illness perceptions of individuals play an important role in the psychological adjustment of individuals suffering from a chronic illness (Abbey, 1993, as cited by Edwards, Suresh, Lynch, Clarkson & Stanley, 2001). A study with clinically diagnosed CFS sufferers has established that illness perceptions can explain a significant variance in levels of anxiety and depression in this population. Specifically, illness identity and perception of illness severity were considerably associated with high levels of anxiety and depression (Dejean, Giacomini, Vanstone & Brindisini, 2013; Edwards et al., 2001; Turner & Kelly, 2000).

5.7. B₁₂ therapy

This crucial theme discusses the effectiveness of B₁₂ therapy, treatment disruption and the request for additional B₁₂ therapy. The majority of the respondents in this study confirmed receiving B₁₂ therapy (93%) and 88% reported starting treatment following the PA diagnosis. Treatment frequency information was specified for 93 respondents, being administered on a frequent basis, mainly between 1-3 months (34%). The main forms of treatment included injections (56%), and to a lesser extent, oral B₁₂ (3%) and topical B₁₂ (1%). In 5% of the cases respondents suggested only having received the loading doses of vitamin B₁₂ and self-treatment (injections) was recorded for 1% of the cases (n=162).

5.7.1 B₁₂ effectiveness

Treatment effectiveness reflects an important element of PA management. However, some individuals are still waiting for the PA diagnosis to be confirmed before treatment is initiated. A minority of respondents stated receiving treatment prior to their PA diagnosis, as a preventative measure from their GPs.

"No current diagnosis. I am currently being tested and on my last visit, I convinced the haematologist to give me a B₁₂ shot to see how I felt. They have booked me in for a follow up visit but I know they are just trying to appease me and I felt absolutely stupid for continuing to question why I was diagnosed for PA in 2003 and why in 2013, I was being told I don't have it, and I couldn't have had it." (Female, 47)

"The doctor said it wasn't PA" (Female, 63)

"The GP suggested starting the B₁₂ jabs before the diagnosis came back for PA as my B₁₂ levels were borderline" (Female, 26)

"Started a year before 'official' diagnosis" (Female, 47)

The majority of respondents felt that treatment was effective, resulting in symptom relief and having a life changing impact on their lives. However, they also expressed being concerned with worsening symptoms, by the time scheduled treatment was due.

"As the injections started I started to feel human, like the old bubbly happy me" (Female, 63)

"I'm alive" (Female, 56)

"After my injection last week my balance has been a lot better and my energy concentration etc. is improved but I don't know how long this will last" (Male, 57)

"Without treatment, individuals with a true diagnosis of PA would experience severe neurological symptoms and eventually the disease is fatal. I feel the regular injections are preventing further neurological damage and also alleviate the other symptoms, such as lethargy and memory issues." (Male, 50)

"Yes. I can think again, my mood has stabilized, my nerves are working right, my fatigue mostly gone, I can eat again without getting sick, and I can lift a pencil without fainting." (Female, 48)

"I am feeling much better but I quickly decline in the couple of weeks leading up to my injections" (Female, 55)

"Yes, I feel much better after the jab and the symptoms start to come back as I am due for the next jab" (Male, 77)

"Yes. I have a buzz of energy for about 2-3 weeks after injection. For about 6 weeks my memory and concentration are better and I don't have sensory loss in my arms/ hands and I don't get pins and needles for about 10 weeks."

(Female, 31)

Considering individuals' accounts, it becomes clear the perceived physical and psychological improvement of symptoms experienced by individuals' as a result of replacement therapy. Some studies have investigated the effectiveness of B₁₂ therapy on the treatment of PA. An early study carried out over a 40-month period confirmed that the administration of parenteral B₁₂ every six weeks in patients with PA resulted in satisfactory maintenance of clinical and haematological remission (Conley, Green, Hartmann & Krevans, 1952). These results are also supported by later studies. A prospective study using patients with B₁₂ deficiency related to PA, found that cobalamin concentration in the blood had increased in 30% as compared to baseline levels, therefore suggesting the effectiveness of B₁₂ therapy (Andrès, Loukili, Maloisel, Vinzio, Kaltenbach, Caro-Sampara & Blicklé, 2005).

Nevertheless, some respondents felt that treatment was not working to the level that they hoped for, experiencing recurrent and severe symptoms.

"No, it is not working I feel like I am slowly getting worse and keep going to doctors but he hasn't a clue and keeps saying I am depressed" (Female, 30)

"No, as I am still having a lot of the symptoms especially the burning pains in my arms, legs and feet" (Female, 37)

"No! I feel lousy, am breathless, ridiculously tired and it is having a detrimental effect on me and my life." (Female. 63)

"No, it is not working, I am short of cash so can't afford to pay privately for enough treatment." (Male, 30)

One of the main reasons for treatment effectiveness in PA may refer to the individual variability in treatment response (Hooper, 2012; Tudhope, Swan & Spray, 1967). Despite regular treatment, B₁₂ stores seem to deplete before next treatment is due, which may explain why many patients still remain symptomatic (PAS, 2009, as cited by McCaddon, 2013; Stabler & Allen, 2004). However, current guidelines do not seem to specify the necessity for individualised PA management (Hooper, 2012).

5.7.2 Treatment suspension

While undergoing treatment some individuals experienced treatment disruption (23%; n=162). The main reasons behind this mainly included their doctors' judgement based on clinical results. Other reasons included socio-economic status and individuals' forgetfulness.

"A few years ago I was given a one off injection and it was never followed up after until I became ill and went to doctors myself to ask for a test" (Female, 47)

"Doctor said my last B₁₂ level was too high as I was self-medicating and has stopped my injections. Doctor also doesn't think I have PA as my parietal cell antibody was negative, but she won't test my intrinsic factor, MMA, active B₁₂ or homocysteine levels and won't accept my word that my symptoms have improved, including measurable hair growth." (Female, 46)

"Now that my B₁₂ levels are 'normal' I'm not getting any injections and have been told to stop taking tablets" (Female, 43)

"Dr. happy with my blood results he stopped all vitamin d, calcium, B₁₂ and iron. I have anaemia as well as I am B₁₂ deficient." (Female, 63)

"I was initially given loading doses and 3 monthly injections, but was told I no longer needed them as I did not have intrinsic factor antibodies." (Female, 26)

"Doctor insisted I should stop for 2 months to see if my levels dropped, which they did." (Female, 58)

"Blood tests showed levels were normal so treatment was stopped. Went downhill rapidly. Had to make a fuss to get treatment started again. This has happened on more than one occasion." (Female, 50)

"My treatment was stopped because of lack of health insurance" (Female, 49)

"I literally forget to get the shot" (Female, 47)

Treatment disruption has been documented in the chronic illness literature, generally with the reduced likelihood of resuming therapy (Harrold, Andrade, Briesacher, Raebel, Fouayzi, Yood & Ockene, 2010). However, this was mainly initiated by patients and referred to reasons such as symptom intermittence (Yeung et al,2013; Kiliñç & Campbell, 2008) side effects, drug ineffectiveness, financial problems (Yeung et al,2013; Harrold et al,2010), inability to get more treatment and inconvenience of treatment (Yeung et al, 2013). According to the statements of PA sufferers, the decision to suspend/discontinue treatment was initiated by their GPs. Research has highlighted the importance of patients' active roles in the decision making process (DH, 2001; GMC, 2001); however, investigations of routine practice usually report low levels of patient participation (Collins, Drew, Watt & Entwistle, 2005). Patients' perception of not accepting their doctors' decision may indicate that future care is compromised (Ziebland, Evans & McPherson, 2007; Collins et al, 2005).

5.7.3 Requesting additional treatment and purchasing OTC treatment

Whilst treatment may help to control symptom frequency and severity, for some individuals it may not be the case, as they didn't find a significant improvement in their symptoms since initiating B₁₂ therapy. The demand for more frequent treatment was a common complaint among those that felt that the current treatment regime was not tailored to their needs.

A great proportion of the population (69%) requested for more frequent treatment and 41% of the respondents confirmed buying OTC treatment (n=148). The outcome of requests is summarised below (Table 5.7.3).

Table 5.7.3

Main observations regarding the request of additional B₁₂ therapy (n=112)

Outcome of requests	Number of participants(n)	Percentage of participants (%)
GP agreed	44	29%
GP refused	28	18%
GP refused due to B ₁₂ levels being within the 'normal' reference range	12	8%
GP reluctant, ordered more tests	3	2%
Still negotiating with GP	2	1%

While some doctors fulfilled their patients' request, others may have felt reluctant to do so. One of the main reasons for denial appeared to be that improvement in symptoms would be similar to a placebo effect. Therefore, some individuals felt the need to buy OTC and/or resort to self-medication.

Also, lack of provision in GP practices in case individuals at some point are unable to get treatment (e.g. holidays), appeared to be another reason to buy OTC treatment. One individual reported that when she told her GP that she self-medicated, her treatment was discontinued by her GP.

"In fact I asked for treatment. I experienced the contact with my GP as a struggle. In the end, I got what I wanted: injections. Still the GP is not convinced it helps me. Well, it does!" (Female, 60)

"Because I need daily shots. I was monitored and the doctor concluded with observation that the B₁₂ was needed daily." (Female, 60)

"I was so desperate that I have considered buying injections online but this was prior finding the sympathetic GP. He talked me out of it and agreed to help me. I had already started using sublingual Methylcobalamin." (Female, 47)

"Absolute worst thing has been trying to get enough B₁₂ from my doctor - it's been like talking to a brick wall and I've had to resort to self-medicating." (Female, 63)

"Doctor cannot provide it as doesn't fit with the guidelines apparently"(Male, 50)

"When I asked for more B₁₂ he turned the monitor towards me with the letter from the neurologist, saying that the neurological damage is now irreversible and looked to see if I was reading the letter, then he shrugged. I felt so bullied and dismissed that I will never return." (Female, 37)

"Most GP's in my surgery simply refused. They spoke to me as though I was neurotic. One agreed to give me an additional injection but said any improvement would be 'psychosomatic'." (Female, 56)

"Tablets didn't help all the symptoms, so I requested injections, was getting worsening symptoms leading up to each injection so requested more frequent injections or the loading doses that I should have had initially (but never got). Doctor refused so I resorted to self-medication and she has now stopped my injections as a result. I cannot even begin to explain how incredibly frustrating this has been. I have provided scientific evidence to my doctor on numerous occasions but to no avail. I'd have been better off refusing B₁₂ blood tests and lying to my doctor about the self-medication." (Female, 48)

"Because I couldn't get it from my doctor and it enables me to live a normal life again! Also it's safe as it's not possible to overdose on it." (Female, 37)

"I could not live on 3 monthly injections. Gradually my mind disintegrated. Extra has helped moods, at least now." (Female, 62)

"I buy transdermal patches to fill in, after having checked with my GP that it is ok to use them" (Female, 49)

"Cyanocobalamin is sold OTC in Canada and is far cheaper than when prescribed" (Male, 65)

"When I was going on holiday and didn't have access to injections. I bought sub-lingual tablets." (Female, 39)

It may not seem surprising that in many cases individuals' request for additional treatment, especially for those who receive quarterly treatment. Experts have stated that in case of PA or severe malabsorptive deficiency, cobalamin resources deplete prior to the 1-month follow-up (Stabler & Allen, 2004).

It has also been suggested that after the dosing protocol, treatment should be administered once monthly for life (CDC, 2009; Stabler & Allen, 2004). As previously mentioned, some physicians still rely on 'the one-size- fits- all' regimen, which negatively affects patients' care.

This apparent lack of flexibility within the healthcare system often encourages individuals to take the responsibility for their own treatment; this may result in health inequalities, when considering those who do not have access to treatment (Hooper, 2012; Pacholok & Stuart, 2011). The main source of B₁₂ supplements derives from internet companies, and some of these supplements have not been subject to testing. However, the risks of purchasing OTC treatment are not yet acknowledged (Hooper, 2012).

5.8 Symptom management

This theme refers to the symptom experience and ways individuals managed their symptoms as well as the inability to control their symptoms. In the majority of the cases (63%), individuals felt they could not control perceived symptoms. The tables below (Fig 5.8.1; 5.8.2) show the frequency and severity of the main types of symptoms experienced by individuals.

Table 5.8.1

The frequency of main symptoms experienced by PAS members

Main symptoms	Symptom frequency					Response Count
	Always	Almost always	To a considerable degree	Occasionally	Seldom	
Shortness of breath	10	9	35	55	38	147
Dizziness	6	11	34	56	38	142
Extreme tiredness	29	33	44	37	7	148
Poor concentration	15	24	47	42	21	149
Confusion	10	11	35	49	42	146
Mood Swings	9	23	37	51	27	147
Pins and Needles	18	21	24	47	35	145
Sleeping problems	26	19	35	43	27	149
Lethargy	33	20	39	41	14	146
Unusual gait	15	10	17	31	66	139

Table 5.8.2***Symptom severity of the main symptoms experienced by PAS members***

Main symptoms	Symptom severity					Response Count
	Not severe	Mild	Moderate	Severe	Very severe	
Shortness of breath	47	38	45	11	6	146
Dizziness	51	31	42	20	2	144
Extreme tiredness	12	22	45	42	31	149
Poor concentration	29	37	41	34	10	150
Confusion	50	36	37	19	6	146
Mood Swings	39	38	38	22	11	145
Pins and Needles	42	32	41	17	14	145
Sleeping problems	34	36	33	23	25	145
Lethargy	22	27	34	35	30	145
Unusual gait	70	21	27	10	12	138

Both tables suggest that the most frequent symptoms perceived by individuals were not necessarily the most severe ones, which may suggest that individuals may have become habituated to experiencing severe symptoms (Jones, Somerville, Feder & Foster, 2010; Turner & Kelly, 2000).

Individuals managed the frequency and severity of their symptoms in different ways. For some, ways of coping concerned relying on treatment or alternative medication, ignoring their symptoms or getting by through lifestyle choices such as resting, eating a healthy diet and practicing exercise. Others did not allow the symptoms to get the best of them, accepted their condition and carried on with their lives.

However, some struggled to lead what they would call as a normal life and suffered in isolation. Others relied on the support from their families and/or support organisations.

"I listen to my body now. When symptoms increase in frequency/severity, I inject more frequently and rest. I hardly ever need to use pain relief now, whereas on the three monthly regime, I took 8 painkillers a day and used a tens machine." (Female, 32)

"I am on antidepressant medication" (Female, 48)

"I self-medicate according to my symptoms, it works" (Female, 41)

"I just count down the days until the next jab I use holidays and sick days to get the rest I need" (Female, 56)

"I do my best to ignore it and my kids have to help me to remember everything" (Male, 77)

"Eat healthily, exercise regularly, attempt to sleep well (occasionally with the use of sleep aids), allow myself to have a decent rest if I am particularly fatigued/worn out." (Female, 49)

"I do not recall much of life before PA. The memory loss makes accepting PA easier." (Female, 66)

"I have accepted that this may take a while to sort out so I am looking after myself and pushing/paying for more tests when necessary." (Male, 50)

"It is a way of life. Sometimes I sit here for hours and hours thinking I am holding a conversation. In reality, I sit here in silence and the conversation is in my head. I find it hard to find the energy to talk, to go out, and to actually do something with my time." (Female, 58)

"Isolation: curl up in a ball in my bed. Stay away from social things." (Female, 29)

"I've just joined the PA Society and hope to learn from others how to cope. Right now, I don't feel as if I'm coping very well at all - I'm just along for the roller-coaster ride." (Female, 56)

"Have a loving husband who takes good care of me in my down times and my tired times. I also meditate and study Buddhism. I am also about to begin graduate school after obtaining my BA. So I put what energy I have into my studies." (Female, 32)

Coping strategies have been associated with either a positive or negative impact one's adjustment to chronic illness. Studies that have suggested positive predictors of social adjustment have included seeking social support, illness acceptance and lifestyle changes (Büssing, Ostermann, Neugebauer & Heusser, 2010; Meijer, Sinnema, Bijstra, Mellenbergh & Wolters, 2002; Yuet, Alexander & Pak Chun, 2002; Ahlström & Sjöden, 1996; Ray, Weir, Stewart, Miller & Hyde, 1993). A study exploring empowerment and perceptions of control in patients suffering from various chronic conditions has reported individuals recognizing the illness was part of them, yet a distinct part of their "selves", therefore feeling a sense of reconciled identity and more control over their illness (Aujoulat, Marcolongo, Bonadiman & Deccache, 2008). Depression, anxiety and low-self-esteem have been previously reported as negative predictors of adjustment to one's illness (Meijer et al, 2002; Yuet et al, 2002; Ahlstrom et al, 1996; Ray et al, 1993). Other studies have suggested maladaptive coping strategies such as escape-avoidance, to contribute to impairments in physical and social functioning (Büssing et al, 2010; Nater, Wagner, Solomon, Jones, Unger, Papanicolaou, Reeves & Heim, 2006; Heijmans, 1998).

5.8.1 Inability to control symptoms

Even though some respondents felt that lifestyle choices could help alleviate their symptoms, the majority believed that they had no control over their symptoms (63%; n=151), expressing great vulnerability. It may be that in some cases individuals felt that PA took control over their lives.

"It is difficult to do anything when the body gives up on you and hard to stay positive when everything causes pain, or you are beyond exhaustion doing simple things." (Female, 51)

"You have no control over it, you just have to grin and bear, it's out of your hands only the doctor can make you feel better by treating you, but when they don't know anything about it, treatment is hard to get." (Female, 58)

"I can't control my symptoms, only the injections can hopefully relieve them. I can help matters though by living a healthier lifestyle and making choices that won't prevent the injections from working to the full potential." (Male, 50)

"Although my symptoms are greatly improved, I still feel that the condition controls me and that I am somewhat helpless." (Female, 49)

Some PA sufferers commented on their perceived lack of control over their condition, mainly attributing it to external causes. Research has documented individuals' experience of powerlessness over their condition, with no perceived resources within themselves to act towards a desired goal (Clarke, Yates, Smith & Chilcot, 2016; Aujoulat et al. 2008). A study by Horner (1996) has found that individuals with an external locus of control were more vulnerable to physical illness and were more likely to have maladaptive coping strategies (emotion-oriented) as opposed to adaptive coping strategies (task-oriented), when compared to individuals with an internal locus of control.

Illness severity has also been suggested to impact on perceived control (Miglioretti, Mazzini, Oggioni, Testa & Monaco, 2008). It has been suggested that people who rate their illness as more severe are found to have less perceived control (Mazzotti, Sebastiani & Marchetti, 2012; Andrykowski & Brady, 1994 ; Helgeson, 1992). These studies imply that the severity of symptoms influence perceptions of low control and the experience of psychological distress.

5.9 Provision of information and support from local health services

This theme includes the perceived support provided by health services in dealing with B₁₂ deficiency/PA and highlights ways of improving this support, from an individuals' perspective. Once diagnosed, 48% of the respondents did not feel they received information from their GP's. 38% felt they were informed about PA and the information provided was perceived as beneficial in 34% of the cases. However, 99% of the individuals confirmed seeking for further information (n=151).

Individuals predominantly searched for online information (53%). This mainly included looking in the PAS website (42%). To a lesser extent, individuals looked for information in libraries (12%), another support organisation (B₁₂d.) and on the NHS website however, this is not surprising since the sample in the current study represents an online sample.

Individuals also thought that healthcare services were somewhat helpful in dealing with their condition (22%). However, 20% thought they were not at all helpful. Results indicated that healthcare services were very helpful in only 2% of the cases.

When asked what was the purpose of GP visits in relation to PA, in 72% of the cases it was related to scheduled treatment, in 32% of the cases, test monitoring, and in 29% of the cases, it was related to PA review. The confidence in discussing PA with clinicians was recorded for 49% of the population as compared to 51% who felt they could not discuss the condition; (n=143).

Respondents provided mixed opinions regarding the quality of support provided by local health services and the availability of health professionals to discuss PA issues. While some felt that they were well informed and that they could trust their doctors, others felt that the information that they have received when first diagnosed wasn't enough and lacked clarity. Therefore, many had to find out more about their condition. At times, health professionals were perceived as being dismissive, resulting in individuals' mistrust and reluctance to make further enquiries. According to individuals' opinions, the lack of understanding and awareness of PA within the medical profession appears to be a detrimental issue.

"My doctor knew how to take care of me" (Female, 66)

"Not old doctor but new doctor starting to trust slowly so being more open with him" (Female, 48)

"I was given very little bar a few leaflets which I lost when I ran to the bathroom to be sick at the horror of being diagnosed with such an illness at such a young age and with no supervision" (Female, 27)

"I had conflicting info from Dr and Nurse" (Female, 32)

"It was just the bare bones of PA, i.e. B₁₂ deficiency caused by lack of intrinsic factor. I would require loading shots and an injection." (Female, 56).

"Because as far as they're concerned the symptoms are fully treated by 3 monthly injections so you feel like a complete fraud questioning it" (Male, 30)

"I can't discuss something that my GP doesn't recognise" (Female, 51)

"My GP has on occasion called me a "silly girl" and has written notes that do not reflect our conversations. The confusion have led me to believe I was not remembering things, so from now on I will attend with notes and my husband if he is available." (Female, 37)

"I feel as if the doctors don't take PA seriously and try to fob me off with stress or depression rather than finding out the cause of all my symptoms" (Female, 45)

"I am not able to discuss my concerns regarding PA unless I bring medical articles ("evidence") that my symptoms could be/are a possible consequence of PA. If I don't bring such "evidence" I'm often told that there is no reason for my concerns." (Female, 58)

"I feel we have reached a limit. I think that she is doing the best she can with the limited information that the GPs in Australia get. I don't think she understands the severe impact it is having on my life." (Female, 71)

"I queried the reaction to high homocysteine and B₁₂ as this is something my sibling has. Answer: don't know we don't test for homocysteine in the UK." (Female, 44)

"I feel Dr. Thinks I am a hypochondriac; I avoid visiting unless I am desperate." (Female, 51)

"They don't listen; they don't understand it and I see a different doctor every time. I've given up and don't even bother anymore!" (Male, 58)

Members of the PA society rated the provision of support in the diagnosis and treatment of PA as very poor in the majority of the cases (25%) and inadequate (20%). Good support was reported in 10% of the cases and very good support in 8% of the cases (PAS, 2011).

Other studies have also reported individuals' lack of satisfaction with the management of their condition, linked with the lack of perceived social support in effective self-management, failure to meet their needs and frustration with the provision of care (Murphy, Chuma, Mathews, Steyn & Levitt, 2015; Snow, Humphrey & Sandall, 2013). These are some of issues also encountered by PA patients.

In some cases, patient satisfaction is evaluated by the provision of informational and interpersonal skills rather than the ability to treat (Deale & Wessely, 2001). Complaints revolved around delay and/or dispute over diagnosis, misdiagnosis, perceiving doctors as dismissive, sceptical, providing inadequate/ conflicting advice, not having enough knowledge about the condition and experiencing unhelpful and distressing consultations. These complaints are also present in other studies (Hooper, Hudson, Porter & McCaddon, 2014; Dickson, Knussen & Flowers, 2007). Patients satisfied with the care provided, perceived their doctors as supportive and interested in their condition. Annandale & Hunt (1998) reported individuals feeling dismissed by their GPs over diagnosis related disagreements and poor doctor-patient interactions in terms of not providing enough information or providing conflicting advice regarding their condition.

Perceptions of being accurately informed, developing illness related knowledge and the meaning attached to the information provided have been found to be very important in the management of the disease, whereas the opposite has been found to be associated to feelings of helplessness (Aujoulat et al.,2008; Kharrazi and Kharrazi ,2005). Implications arise regarding the doctor-patient therapeutic alliance, being central to the effective management of a complex illness such as PA.

5.9.1 Suggestions for improving the availability and quality of local health services

While some individuals may have felt privileged with the care provided from their local health services, the majority felt the need of its improvement. PAS members provided suggestions, which they believed, would make a difference to the current management of PA. This included training of health professionals, treating each patient as unique, developing better protocols to ensure an early diagnosis and provide additional care beyond the physical aspects of the condition. This could potentially result in improved experiences in the clinical encounter as well as reduce health costs at a great level.

"I am extremely fortunate to have an approachable and supportive GP/Practice Nurse, and therefore I can't think of any ways of improving the service which I have personally received in relation to my diagnosis of PA." (Female, 39)

"My own doctor has been extremely helpful but I know this is not at all typical" (Female, 42)

"GPs' need re-educating in B₁₂, most are dangerously unaware of the facts about the illness and the best ways to diagnose/treat it. I have been shocked by some things doctors have said to me and I have been very distressed to think that others would be blindly following this disaster, lushly wrong advice from a person you trust." (Female, 43)

"They could listen to me and how I feel. They should not be adopting the 'one size fits all' approach, as this may be the cause of more costly treatment. One Hydroxocobalamin injection = a few pence. The results of not having enough B₁₂ runs into thousands of pounds, it is false economy! They need to develop a blood test for B₁₂ at cellular level, not just test for the amount present in the blood. This could potentially save the NHS millions of £'s and they are stupid not to do it!" (Female, 51)

"I was never offered any information about pernicious anaemia, I never saw the Doctor concerning my PA, and the nurse who gave me the injections seemed to have very little knowledge about it. When diagnosed I think the patient should be seen by the Doctor to have PA explained and not leave it to his staff who have very little or no knowledge of the condition." (Female, 49)

"To use active listening skills and if after repeat complaints of the same symptoms over a two year span, that they seek out other areas of diagnosis to find out what is going on with their patients." (Female, 58)

"I am in Canada, my health system fails miserably. Again, this is because PA is an orphan illness, there is a (sort of) treatment, it is cheap and sort of does the job in keeping one alive. However, it falls through the cracks in every sense. There is no PA speciality and PA is not glamorous, will not get anyone a great fat grant, etc. Health services should address the issue of these rare orphan illnesses generally; there should be protocols for PA sufferers to be seen by every speciality involved at least when diagnosed." (Female, 45)

"There is rarely an opportunity to discuss the emotional effects of PA." (Female, 42)

"Listen to me, treat me as an individual and not a statistic in a guideline book."
(Male, 50)

"It is down to sheer luck of seeing one competent GP that I have been diagnosed. Others have sent me away either calling hypochondriac or suggesting oral vitamin supplements that do not work. I can't believe that something so obvious has been consistently missed." (Female, 42)

" Early diagnosis, better care after diagnosis especially when other conditions have developed as a result of undiagnosed PA, better guidelines and clearer patients' rights when GP care falls below acceptable standards; Health service should take more responsibility for incorrect/late diagnosis and make sure that patients are not left fending for themselves." (Female, 66)

"It would be very beneficial if the GP's surgeries could start running PA clinics in the same way that they run other clinics such as asthma and diabetes."
(Female, 46)

Research has previously reported patients' perceptions regarding how the management of chronic illness may be improved. Barriers to health care improvement mainly include lack of knowledge, training and poor communication in the medical encounter (Maimela et al., 2015; Houle et al., 2012; Mirzaei et al., 2012). A qualitative study addressing health professionals' perceptions on the management of hypothyroidism emphasised lack of expert knowledge, lack of patient education and over-reliance on clinical tests as main contributors to the suboptimal treatment of hypothyroidism in general practice (Dew et al., 2018). The need to factor in patient experience is vital to provide a holistic approach to the management of chronic illness (Coulter, Roberts & Dixon, 2013; Yen et al., 2011).

5.10 Relationships

Individuals commented on the inability to manage PA on a daily basis, causing strains in their personal and social lives. This theme discusses both intimate and social relationships.

5.10.1 Intimate and social

The working lives of these individuals have been negatively affected. Personal relationships were transformed and emotions were very fragile. Individuals felt they underperformed at work, having to take time off to cope with symptoms and restore their energy.

"Struggling to get back to full health and feel no energy to do nothing, it is a constant struggle every day." (Female, 49)

"Have had to take time off work with symptoms as unable to carry out duties when at worst and I have been turned down for jobs and experienced disciplinary due to sickness absence."(Female, 55)

"I cope poorly. I have to take a lot of time off, and perform at very low levels for work and in a social capacity. My bedtime is 8:30-9pm." (Female, 47)

"It has affected how I feel on a day to day basis, I get very depressed and frustrated, it has affected my job, my career, relationships, social life, starting a family, things like going away and doing things...feel like a decrepit old woman, not able to live the kind of life most people do at my age, and that I would have wanted to." (Female, 27)

"Yes in every way - I think my friends all think I'm mad as well they have had enough of me moaning about my health. My work has become more difficult; I find it hard to concentrate for any length of time." (Female, 37)

"I would like to be able to keep up with my friends and family, but I can't. I am tired. I forget things a lot. I have about a week to 10 days each month (right after my injection) where I feel great and could conquer the world. Then it peters out." (Female, 51)

"I've gone down to only working part time, I am unable to go out socially as often as I used to, I've drifted away from friends, etc.; and the symptoms affected my relationship." (Male, 30)

"My family are affected by the restrictions this has put on me, my mood swings and irritability." (Male, 50)

"Concentration affects my school work; my tiredness affects my playfulness with my son, and my mood swings make other people unhappy." (Female, 32)

"I fake that I am happy in social settings. I fake that I am getting my work done but I really cannot focus. It is difficult to be taken seriously at work when you literally cannot string a complete thought together in a group setting (makes me want to cry). My memory is so affected that I forget things moments after they are spoken about... I laugh along, yeah it's hell getting old, but I know that's not the cause." (Female, 42)

"As I am often too tired to socialise I don't have many close relationships. I recently attended college and found it very hard to retain information when sitting exams. I am finding it hard to find a new job as I don't think I could handle full-time work." (Female, 19).

Ell (1996) has reported the substantial impact that chronic illness places on families. Experiencing emotional strain, physical demands, fear, uncertainty, altered roles and lifestyles, all may significantly influence marital relationships, the family system and alter the social reality of a family.

Studies have documented negative relationship interactions between individuals suffering with a long-term condition and their partners, resulting in distress (Golics, Basra, Finlay & Salek, 2013; Wittenberg, Saada & Prosser, 2013; Waxman, Tripp & Flamen Baum, 2008; Rook 1990).

Individuals' perceptions of having a caring and supportive relationship also reflect the absence of conflict (Robinson, 2017; Luttik et al., 2005; Coyne & Bolger, 1990). Literature has also pointed out the positive effects that social support plays on morbidity and psychosocial adaptation. Positive aspects relate to increased general well-being and a substantial decrease in depressive states (Trief, Sandberg, Greenberg & Weinstock, 2003; Ell, 1996; Revenson et al, 1991). Participation in employment has been reported as the main road to well-being. Work reflects an important area of an individual's life that gets affected with the presence of a chronic illness (van Campen & Cardol, 2009). Dealing with the emotional impact of a chronic illness may prove uncomfortable for many people. The consequences are withdrawal from social activities and professional relationships, resulting in a restrictive life fostered by insecurity (Aujoulat et al, 2008). Individual satisfaction is integral to social adjustment (Waxman, Tripp & Flamenbaum, 2008).

5.11 The impact of PA on one's life

The super ordinate themes mentioned in this study revolve around and seem to directly affect sufferers' everyday lives. The majority of the respondents suggested that PA impacted on their daily lives (92%) with 81% experiencing lifestyle restrictions as a consequence of having PA (n=136).

The detrimental effect of B₁₂ deficiency/PA has been essentially expressed through the severity of symptoms and the inability to manage these. Individuals felt they did not have control over their bodies and even the most usual and minor tasks were difficult to attain. Furthermore, their sense of identity appeared to be fragmented.

"I do not have a quality of life. I am unable to go shopping as I cannot cope in busy surroundings and have difficulty with walking." (Female, 58)

"Walking, sleeping, breathing, inability to carry out the simplest of tasks, the overwhelming exhaustion, I could go on and on." (Female, 49)

"Working, housework, anything that requires concentration or energy" (Female, 47)

"I am not me anymore, just a sad old woman." (Female, 63)

"I am not the same person. I can't work or concentrate. My life is forever changed." (Male, 50)

"It has been a struggle to lead a normal life and cope with exacerbated symptoms." (Female, 37)

For individuals who experience chronic illness, maintaining a good quality of life is essential for disease management and improved psychosocial outcomes (Davison & Jhangri, 2013; (Megari, 2013; McGee, 2001). Studies have found impaired HRQOL to be an important predictor of co-morbidity presence (Huber, Wacker, Vogelmeier & Leidl, 2015; Kluger et al., 2014; Hussain et al, 2001). Impaired quality of life has been associated with frequent and severe symptomatology, distress, functional impairment, poor psychological well-being and mood disturbances (Blinderman et al, 2009). Living with a chronic illness may also influence one's sense of identity (Aujoulat et al, 2008). A study by Larun & Malterud (2007) with CFS sufferers has suggested that the experience of symptoms and stigma from significant others posed a threat to individual's identity. In this study, patients felt blamed and dismissed which in turn led to withdrawal and behavioural disengagement, having a detrimental effect on HRQoL.

Nevertheless, studies also report the beneficial role of illness acceptance in improving HRQoL (Mroczek, Parzuchowska, Jasińska-Starczewska, Grodzki & Kurpas, 2017; Kurpas et al., 2013). In light of this, focusing in improving the management of PA may result in the enhancement of the overall quality of life in these patients.

5.12 General discussion

The present study sought to investigate the experience of a B₁₂ deficiency/PA diagnosis through the perspective of members of the PAS. The main findings of this study highlight issues with diagnosis and treatment that have been discussed in previous literature (Devalia, Hamilton & Molloy, 2014; Hooper, Hudson, Porter & McCaddon, 2014; Carmel, 2008) as well as in study 1 and 2. This relates to the occurrence of misdiagnosis and suboptimal testing and treatment. However, the current study adds to existing findings by offering more insight in terms of the frequency and severity of symptoms experienced by this population, symptom control, the main sources of information pursued to aid illness understanding and information regarding OTC treatment. Data suggested that the main symptoms of, extreme tiredness, poor concentration, pins and needles, difficulty sleeping and lethargy, were experienced more frequently and to a moderate degree, however these were not necessarily rated as more severe. Inspection of time since diagnosis in relation to symptom frequency and severity seemed to indicate that symptoms were rated as more frequent and severe in patients with a time since diagnosis between 1 and 5 years. This was not noticed in patients with a longer time since diagnosis (> 10 years). This may indicate that individuals may have become used to deal with these symptoms (Jones, Somerville, Feder & Foster, 2010; Katon, Sullivan, Walker, 2001). In addition, these symptoms may be related to existing co-morbidities, which was reported for a great proportion of the population (75%).

Individuals also suggested that health professionals perceived their symptoms as being psychosomatic in nature, resulting in patient distress and resulting in problematic medical encounters (Armstrong, Rochnia, Harries, Bundock & Yorke, 2017; Banka, Ryan & Thomson, 2011; Devalia, 2006; Deale & Wessely, 2001).

The inability to control symptoms was also reported by the majority of the respondents (63%). Lack of control over symptoms in chronic conditions has also been reported elsewhere, being associated with increased symptom severity (Clarke, Yates, Smith & Chilcot, 2016; Aujoulat et al. 2008). In terms of searching for PA related information, results suggest that 99% of the population searched for information to supplement the information provided by their GP's. Most of this information was pursued online mainly in the PAS website. The increased use of the internet to research health concerns has been documented (Armstrong, Rochnia, Harries, Bundock & Yorke, 2017; Liddle et al., 2015; Diaz et al., 2002), and this would be expected given the nature of the sample in the current study. A study looking at patients' use of online sources (NHS and WebMD websites) to check their symptoms indicated that the diagnoses suggested in relation to the presenting symptoms were frequently inaccurate (Powley, McIlroy, Simmons & Raza, 2016).

Another study investigated whether the identification of symptoms in online sources would provide information for users to seek appropriate health care. This study identified several online websites through Google, Yahoo and Bing search engines. Findings suggested that these websites provided poor information, lacking in prescriptive guidance, therefore not effective to aid decisions about whether symptoms presented required urgent attention (North et al., 2012).

The results of this study are similar to another study assessing the clinical performance and triage accuracy across a large number of symptom checkers. These were based in the UK, United States, the Netherlands and Poland, and were checked against standardized patient evaluations concerning common and uncommon conditions. Deficits were found in listing the correct diagnosis and for triage decisions (Semigran, Linder, Gidengil & Methrotra, 2015).

The overreliance in seeking online information results in the unsuitable use of health care services and more importantly influences how patients respond to advice. This has implications for the current study findings, as it is unclear the extent to which PA diagnoses are self-diagnoses, which may result in the increased self-management of the condition without correct advice (Janevic et al., 2014; Schulman-Green et al., 2012; Lessenger, & Feinberg, 2008). A significant proportion of the respondents confirmed buying OTC treatment to top up their current treatment, when unable to get the treatment they expected. However, only 10% of the individuals (n=156) confirmed exclusively self-managing their condition.

The qualitative component of the present study relates to six superordinate themes, which include misdiagnosis, PA diagnosis, B₁₂ therapy, symptom management, provision of information and support from local health services and relationships. These themes reflected loss of identity as part of individuals' journeys, significantly affecting individuals' lives. These qualitative findings are very similar to study 2 as well as findings from various chronic illness studies (Robinson, 2017; Hooper, Hudson, Porter & McCaddon, 2014; Golics, Basra, Finlay & Salek, 2013; Dickson, Knussen & Flowers, 2007).

Nonetheless, the current study expands on information regarding the feelings experienced because of misdiagnosis, emotional responses from being diagnosed with PA, treatment suspension and ways of improving the management of PA from a patients' perspective. Research has previously documented feelings of being misdiagnosed (Duck et al.,2015; Barais et al.,2014; Aujoulat et al.,2008) as well as emotional responses associated to receiving a diagnosis (Armstrong, Rochnia, Harries, Bundock & Yorke, 2017;Sexton & Loflin 2009; Lehman et al.,2002).

Treatment suspension represented an important sub-theme bearing implications for clinical practice. It was suggested that patient care was compromised when clinicians decided to interrupt treatment, despite PA diagnosis. This may reflect lack of understanding regarding the management of PA, a common observation of patients with the condition (Hooper, Hudson, Porter & McCaddon, 2014). Further, individuals reported not feeling confident to question medical decisions regarding treatment. Reasons for this may be related to the level of trust placed on the medical profession, resulting in poor communication (Maimela et al., 2015; Dickson, Knussen & Flowers, 2007). Suggestions to improve the availability and quality of local health services reflected the need for training of health professionals, the need to provide multidisciplinary support and to manage PA from a holistic point of view. Patients felt that healthcare professionals "had little appreciation for those aspects of illness beyond the realm of what biomedical science makes rational "(Thorne, Nyhlin & Patterson, 2000, p.306). This is not uncommon in the management of chronic illness when considering the challenging demands of treatment, financial pressures and co-morbidity (Yen et al., 2011).

Even though time since diagnosis varied between PAS members', their illness perceptions did not seem to be dissimilar. Challenges faced by individuals as documented in previous research, still reflect current issues in the management of PA (Devalia, Hamilton & Molloy, 2014; Hooper, Hudson, Porter & McCaddon, 2014; Carmel, 2012; PAS, 2008; Devalia, 2006). The themes that surfaced from the current study findings highlight perceptions of treatment as vital in the improvement of symptoms, influencing positive illness responses and contributing to improved quality of life.

Alternatively, the lack of perceived support in getting treatment and/or receiving tailored treatment contributes to individual psychological distress and subsequently illness responses that may not be adaptive and therefore detrimental to quality of life. These themes that emphasize the relationship between illness perceptions, health status and coping responses will serve as foundations to the measurement of the aspects of illness that are meaningful to this population group. To address the potential limitations of the current study, the forthcoming study (4) will recruit patients from local GP surgeries to ensure that the findings are representative of the PA population. Given the central role played by clinicians regarding patients' journeys to diagnosis, future research should also include their perspectives regarding the management of B₁₂ deficiency/PA.

The design of the current study was flexible, allowing for data collection of a distinctive population. The PAS members represented a varied sample in terms of ethnic background, with varied age groups, being active members of a support system. Patient organisations such as the PAS empower individuals and help reduce the stigma of being diagnosed with PA (Hooper, 2012).

It may be reasoned that individuals' belonging to support groups may feel more in control of their condition. Therefore, their views may be more assertive in comparison to the views of individuals who do not engage with support groups (Grande, Myers & Sutton, 2006; Voerman et al., 2006). However, in terms of illness experience, PAS members' experiences didn't seem to be that dissimilar to the ones of individuals' with no membership to support groups, as in study 2. Perceived lack of control over their illness and the difficulty in dealing with everyday life challenges were reported by many individuals in the current study.

Informational support may represent a key factor contributing to the illness understanding of PAS members. This may have helped some individuals to be more active in terms of developing awareness of the condition, conveying their needs to their GP's and/or making decisions regarding the self-management of their condition.

The current study provided a neutral environment for individual responses, reducing the potential stigma that individuals may face. However, it may be limited by self-selection bias as well as it may have also missed accounts of individuals that do not have access to the internet (BPS, 2013; Wright, 2005). Nevertheless, this sample provided substantial evidence that is well supported by previous research conducted in the area of chronic illness, by existing PA research and the findings of preliminary studies (study 1 and 2).

The study presented here expands on the growing body of PA knowledge by emphasizing the need to measure psychosocial variables. The experience of ongoing symptoms and variability in response to treatment may result from different factors such as time since diagnosis, the way individuals perceive their condition, the way they cope, the potential tendency to somatise symptoms and associated risk for anxiety/depression. To date, studies presented in this thesis have been of an exploratory nature. Therefore, the forthcoming study (study 4) aims to measure illness perceptions, health status, coping strategies, locus of control and somatic focus and investigate to what extent these variables may form the basis of a patient-centred tool for the identification and management of health-related quality of life in this population. B₁₂ deficiency constitutes a major public health problem and currently there is a lack of awareness within the medical profession to identify and treat PA (Carmel, 2008).

Further, current guidelines may not be explicit to reflect individual treatment needs (Hooper, 2014). Since there is no tool to assess the severity of patients' symptoms, developing a condition-specific tool in a new area of clinical research may prove valuable to patients by providing tailored treatment, therefore improving health-related quality of life. It may also benefit health professionals, by providing information that may potentially be used as basis for referrals.

5.13 Reflexive analysis

Before the start of the current research, I joined the PAS to access the members' forum. After the survey was posted online, I have perceived members' defensiveness concerning the nature of the research being conducted. I am aware that investigating PA perceptions may have triggered prior negative experiences such as patients' symptoms being addressed by clinicians as psychosomatic in nature. This represented a challenge in terms of being able to address potential lay understandings regarding the focus of research. Hence, any future research conducted with this population considered this aspect by using unbiased wording when informing or providing feedback regarding the research outcome.

Considering that the present study was a web-based survey, it may have reduced the likelihood of the data collection process being affected by the presence of the researcher. I have ensured that each involved question presented to participants did not represent a theme in its own account. A report of the findings of the current research was posted by the Chair of the society in the members' area. Feedback regarding these findings was approached with great positivity and it was mentioned that these findings helped strengthen preliminary research conducted by the PAS. This feedback has helped to ensure that the current study findings provided rich detailed information, being reflective of individuals' experiences.

Members of the PAS may have had increased expectations of improved healthcare from participating in this research. While this is difficult to avoid, I ensured that the main purpose of the research was to further the understanding of PA. Increasing awareness regarding the issues faced by PA sufferers may contribute to improved management of this condition.

Chapter 6

Study 4: Investigating illness severity and health-related quality of life in patients diagnosed with Pernicious Anaemia

6.1 Study Aims

The primary endpoint of the present study is to develop a patient-centred outcome measure for the identification and management of health-related quality of life in patients suffering with pernicious anaemia. The secondary endpoint is to identify the best predictors of HRQoL in this population.

6.2 Background

Existing PA research has primarily approached issues regarding the diagnosis and treatment from a medical point of view. Pilot work presented in this thesis, highlighted patients experiencing severe symptoms, resulting in major life disruptions. For many patients, symptom management through B₁₂ therapy appears to be suboptimal (Hooper, Hudson, Porter & McCaddon, 2014). The goal of PA treatment is to limit symptoms, delay the progression of disease and optimise one's health-related quality of life. Assessing the impact of PA on one's life is key to establishing the severity of one's condition. Health-related quality of life measures provide an understanding of how an illness impacts on one's daily living. Employing generic measures allows the comparison of HRQoL across different conditions. However, generic measures assess quality of life independent of condition-specific characteristics; therefore, important illness aspects such as the experience of symptoms may be overlooked.

Condition-specific measures possess the advantage of capturing subjective evaluations that are appropriate to the illness under study (De Gutch, 2015). Most conditions have a HRQOL measure to assess the illness burden (Bradley, Todd, Gorton, Symonds & Plowright, 1999; Wong, Guyatt, Cook, Griffith & Irvine, 1998; Juniper, Guyatt, Epstein, Ferrie, Jaeschke & Hiller, 1992). However, very little is known regarding the HRQoL of patients suffering with pernicious anaemia. There is a gap in research addressing the psychosocial impact of PA on individual's adjustment. Therefore, it is anticipated that developing a patient-centred instrument for the identification and management of health related quality of life in patients suffering with PA would further the current understanding of this condition. Clinicians' accounts fail to capture the impact of disease from a patient's perspective (Heijmans et al., 2001). To improve one's quality of life there is a need to identify modifiable determinants, and illness representations have been suggested as valuable determinants of an individuals' quality of life (Schoormans et al., 2014). Explanations for the variability in responses to a health threat have been put forward by the common sense model developed by Leventhal (Leventhal, Meyer and Nerenz, 1980). The central principle of this theory refers to the impact of illness representations on individual's coping responses, which in turn may influence judgement-based outcomes such as emotional reactions and quality of life (Llewellyn, McGurk & Weinman, 2007). According to this model there is a consistent pattern in the way individuals' organise their illness perceptions and this refers to illness identity (type of illness and associated symptoms), cause of the illness and how long it will last, beliefs regarding personal consequences of the illness for both the individual and their family, as well as the extent to which an individual feels that they have control over their illness.

The Common sense model has been successfully applied in a variety of conditions from Irritable Bowel Syndrome (IBS;Rutter & Rutter, 2002) to Cystic Fibrosis (Sawicki, Sellers & Robinson,2011), Chronic Fatigue Syndrome (CFS;Moss-Morris, Petrie and Weinman ,1996), Multiple Sclerosis (MS; Vaughan, Morrison & Miller, 2003) and Congenital Heart Disease (CHD;Schoormans, Mulder, Melle, Pieper, Dijk, Sieswerda, Hulsbergen-Zwarts, Plokker, Brunninkuis, Vliegen & Sprangers, 2012).

Illness perceptions, psychological status and quality of life, were explored in a sample of 102 outpatients suffering from inflammatory bowel disease. This study employed a disease- specific HRQoL measure for this population. This questionnaire covers specific symptoms as well as emotional status, activities of daily-living, personal interaction and social performance. Findings suggested positive associations between dimensions of quality of life (bowel function, social function, emotional function and systemic function) with timeline perceptions and treatment control. Individuals' beliefs that their illness would last a short time were associated with better HRQoL. Patients' beliefs that medication controlled their condition reported improved quality of life. Alternatively, patients who did not perceive that medication controlled their illness were more likely to present with depressive symptoms (Rochelle & Fidler, 2012). Negative correlations were also found between depression, personal control and emotional function. Individuals who felt they did not have any control over their illness reported experiencing more depressive symptoms. A prospective longitudinal study reported depression and anxiety as significant predictors of HRQoL in patients who were admitted to hospital as a result of experiencing chronic obstructive pulmonary disease. This study used the WHOQOL-BREF as a measure of HRQoL.

Depression was significantly associated with worse psychological and environmental health at baseline, and follow-up (at 6 and 9 months), (Andenaes et al., 2006). Another study explored associations between defensive coping and HRQoL in patients with chronic kidney disease. Defensive coping was assessed using the rationality/emotional defensiveness scale and the 36-item short-form survey served as the general measure assessing HRQoL. Higher defensive coping was associated with worse mental health. A higher score on defensive coping indicated better physical health.

Studies that lend support to previous findings have explored associations between illness beliefs, measures of health status, coping and adjustment. Rutter and Rutter (2002) measured the illness representations, health status, coping and perceptions of quality of life in two-hundred and nine irritable bowel syndrome sufferers recruited from an IBS self-help network. Respondents who felt that their illness had serious consequences reported less satisfaction with health, higher levels of anxiety, depression, and poor quality of life. Individuals who had weak control beliefs stated lower satisfaction with health, greater depression and poorer quality of life. Individuals who believed that their illness was caused by stress reported higher levels of anxiety and depression. In this study, serious illness consequences were associated with the coping strategies of “venting emotions”, “restraint” and “mental and behavioural disengagement”. Acceptance of the illness was associated with reporting fewer illness consequences. A belief that the illness would last for a short period of time was positively related to “seeking instrumental support” and negatively associated with illness acceptance.

Anxiety and depression were both related to a belief in psychological causes and serious illness consequences. Depression was also linked with perceptions of low control. Another study including ninety-nine Multiple Sclerosis (MS) sufferers explored the predictive value of illness beliefs in determining outcome as measured by illness intrusiveness, physical functioning, depression, anxiety and self-esteem. Findings suggested that participants associated MS with a wide range of symptoms that would last for a long time, with no specific cause and unlikely to be cured. Participants felt that they could not control MS and that it had a detrimental impact on various facets of their lives. The belief that MS had serious consequences was associated with higher levels of illness intrusiveness, greater impairment in physical functioning, reduced self-esteem and higher levels of anxiety and depression. An important finding of this study implies that the perception of experiencing severe symptoms, perceiving severe consequences for one's life, perceiving the illness to last a long time and experiencing low control over MS, predicted high levels of depression (Vaughan, Morrison & Miller, 2003). Leventhal's model has also been useful in describing how individuals respond to somatic symptoms regardless of their aetiology. The model suggests that individuals tend to develop a cognitive and emotional representation that elicits behaviours to cope with these type of symptoms (Broadbent, Petrie, Main & Weinman, 2006; Leventhal, Brissette & Leventhal, 2003, as cited by Zhang, Fritzsche, Leonhart, Zhao, Zhang, Wei, Yang, Wirsching, Nater-Mewes, Larisch & Schaefer, 2014). A study by Zhang and colleagues (2014) has investigated the relationship between somatic symptom severity, quality of life and psychobehavioural characteristics (e.g. illness worries, catastrophizing and avoidant behaviour).

This study aimed to explore how patients with high somatic symptoms differed from patients with low somatic symptoms in terms of illness perceptions and illness behaviour, emotional distress (anxiety and depression) and quality of life; High somatic symptom severity was significantly associated with catastrophizing and illness vulnerability; low physical quality of life was associated with avoidance of physical activity and low mental quality of life was associated for the need of immediate medical assistance. Results also suggested that illness worries and dysfunctional illness behaviour (e.g. safety seeking, repeated doctor visits and fear avoidance) were associated with high somatic symptom severity and poor quality of life (Zhang et al., 2014).

Research studies previously outlined have addressed the importance of illness beliefs in the understanding and management of chronic illness; however, existing research may not be significant to the PA population since the targeted focus of disease-specific investigations is what makes them clinically relevant (Razvi, McMillan & Weaver, 2005). The identification of disease-specific factors that influence HRQoL and enable health professionals to tailor treatment according to individual needs is central in improving the quality of care, optimising clinical outcomes. Research has previously suggested that including validated measures as basis for the development of HRQoL measures, reflects good practice (Kamudoni, Mueller & Salek, 2015). The present study aims to administer quantitative measures to participants to validate the psychological constructs (illness representations, coping, health status, somatic symptoms, locus of control and health-related quality of life) that frequently emerged from pilot work.

These measures will ultimately be subjected to data reduction techniques to identify meaningful variables that may explain HRQoL and its determinants in this population. The study proposed here, being conducted in a 'real-world' setting, has the potential for a more effective approach to patient engagement and satisfaction with treatment.

The development of a HRQoL instrument, built from a patients' perspective, will enable clinicians to understand patients' health status, which may result in improved PA management. In this way, treatment may be adjusted according to patients' needs, resulting in improved HRQoL. Hence, the present study will describe the development of a condition-specific questionnaire for the identification and management of health-related quality of life in patients suffering with pernicious anaemia.

6.3 Methodology

6.3.1 Design

The present study employed a cross-sectional survey design as the basis for data gathering and subsequent development of a screening/outcome measure for patients with PA. Statistical analyses were performed to establish relationships between the variables (Pearson correlation coefficient), to identify predictors of adjustment (Multiple Regression methods) and ultimately to identify meaningful items (Principal Components Analysis) in the dataset.

Variables recorded included ethnic background, source of patient recruitment, marital status, employment, affiliation to support groups, type of diagnosis, family history, time since diagnosis, treatment related information and co-morbidities. Psychological measures included illness representations, health status, multidimensional health locus of control, somatic focus, coping strategies and health-related quality of life.

6.3.2 Ethical considerations

The Abertawe Bro Morgannwg NHS Trust, the North-West Lancaster Research Ethics committee and the University of South Wales, Faculty Ethics Research Sub Group, granted ethical and governance approvals. Regarding the online sample, anonymity of potential participants was secured as Survey Monkey did not retain or transfer IP data with the provided responses. Informed consent procedures were met by all study participants.

6.3.3 Sample

The purposeful sample consisted of 184 patients diagnosed with B₁₂ deficiency/PA (N=184; 144 females, 40 males; *Mean age* = 56, *SD*=16.1). It included patients registered in two GP surgeries (Bridgend and Port Talbot) as well as non-NHS participants, recruited via Social Media websites (PAS and subsidiary groups, the University of South Wales intranet and Facebook pages). Participants were required to be at least 18 years of age, to have received a formal diagnosis of B₁₂ deficiency/ PA from a health professional and to be in receipt of regular B₁₂ injections. The same criteria applied to the online sample and further asked participants to confirm that they were not taking part in this study through their local GP practice. Patient data that did not meet the inclusion criteria were excluded.

6.3.4 Sample size

The current study used an adequately powered sample for conducting the analyses. As a rule of thumb, multiple regression analyses require at least 10 cases per predictor in the model (Field, 2009). It has been recommended that when testing the overall model fit, one would look into the sample size for an overall model (a sample size of $50+8k$, k representing the number of predictors) as well as the sample size for each individual predictor ($104+k$). By calculating both sample sizes, one would select the one with the largest value in the regression analyses (Green, 1991). To conduct an Exploratory Factor Analysis (EFA), an acceptable sample size may be determined by the nature of the data (Field, 2009).

Authors recommend looking at the proportion of variance of an individual variable shared with other variables, and the level of item communality. In the present study, most item communalities were greater than .5, indicating the adequacy of the sample size (MacCallum, Widaman, Zhang & Hong, 1999).

6.3.5 Materials

Brief COPE Inventory (Carver, 1997)

The Brief COPE is a validated, multidimensional short-form of the COPE inventory (Carver, 1989) which has proven to be useful in health-related research possessing good psychometric properties (Tuncay, Musabak, Gok & Kutlu, 2008; Lode, Larsen, Bru, Klevan, Myhr & Nyland, 2007; Carver et al., 1993). Data from the original scale supports the reliability of the reduced scales ($\alpha > .50$). This scale assesses a broad range of coping responses across 14 coping scales (28 items). Both adaptive and maladaptive coping strategies are included (Appendix 4.13). Ways of coping include both cognitive and behavioural strategies such as active coping, planning, acceptance, reframing and behaviour disengagement. Scores for each subscale range from 2 to 8; higher scores indicate more frequent use of a specific coping strategy.

Cronbach's alpha for each subscale ranged from acceptable to high (self-distraction $\alpha = .60$; active coping $\alpha = .81$; denial $\alpha = .73$; substance use $\alpha = .92$; emotional support $\alpha = .81$; instrumental support $\alpha = .72$; behaviour disengagement $\alpha = .66$; venting $\alpha = .72$; positive reframing $\alpha = .61$; planning $\alpha = .85$; humour $\alpha = .71$; acceptance $\alpha = .72$; religion $\alpha = .83$; self-blame $\alpha = .73$).

Multidimensional Health Locus of Control Scale (MHLC; Wallston, Wallston & Devellis, 1978)

This scale has been adapted from the general LOC and may be administered to individuals with a specific health/medical condition (Basinska & Andruszkiewicz, 2012; Nagy & Wolfe, 1983). This scale measures the extent to which an individual believes that external factors (i.e. other people and chance) and internal factors (i.e. one's behaviour and thoughts) play important roles in determining one's health. Sample items include: "If I take the right actions, I can stay healthy" (internal); "No matter what I do, if I am going to get sick, I will get sick" (chance), and "My family has a lot to do with my becoming sick or staying healthy" (powerful others), (Appendix 4.14). The MHLC Comprises of 18 items in a 6- point Likert Scale and possesses acceptable levels of internal reliability ranging from .67 to .76. The Cronbach's alpha values were recorded for each subscale (internal $\alpha=.65$; chance $\alpha=.68$; powerful others $\alpha=.75$)

Patient Health Questionnaire (PHQ-15; Kroenke, Spitzer & Williams, 2002)

The PHQ-15 measures the extent to which patients are bothered which symptoms during the previous 4 weeks. It consists of 15 somatic symptom clusters measured in a 3-point Likert scale (0 "not bothered at all", 1 "bothered a little" or 2 "bothered a lot"), (Appendix 4.15). Scores range from 0 to 30 representing the grading of somatisation disorder. Scores of ≥ 5 , ≥ 10 , ≥ 15 represent mild, moderate and severe levels of somatization. The PHQ-15 possesses high levels of reliability and validity and is proposed to aid clinical judgement and reflect the illness experience of individual patients (Kroenke et al., 2010).

Validation studies have reported the internal reliability (.80) and test-retest reliability (.83) of this scale (van Ravesteijn et al., 2009; Kroenke, Spitzer & Williams, 2002). The internal reliability of the scale ($\alpha=.83$) was recorded for the PA population.

The Brief illness perception Questionnaire (Brief IPQ; Broadbent, Petrie, Main & Weinman, 2006)

The Brief IPQ represents a shorter version of the IPQ-R (Moss-Morris et al., 2002), a widely used scale to assess patients' representations of their illness (Broadbent, Wilkes, Koschwaneza, Weinman, Norton & Petrie, 2015; Afshar et al., 2011; Dalbeth et al., 2011; Broadbent, Ellis, Thomas, Gamble & Petrie, 2009; Dickson, Toft & O'Carroll, 2009). The Brief IPQ provides the option to adapt question wording to the specific illness being investigated. This scale includes a total 8 components in which 5 of these assess cognitive illness representations (consequences, timeline, personal control, treatment control and identity); 2 items that represent emotional representations (concern and emotions); 1 item assessing illness understanding and 1 item assessing causal representations (Appendix 4.16). Identity refers to the label individuals use to describe their illness and the symptoms they view as being part of the condition; consequences refers to the expected effects and outcome of the illness; timeline relates to how long the patient believes the illness will last, and control the extent to which individuals believe that they can recover or control the illness. The emotional representation includes negative reactions such as distress and fear. Items are rated on a 0-10 response scale except for the "causal" component where items may be grouped into categories determined by the specific illness and a categorical analysis may be performed.

A total score may also be computed, representing the degree to which the condition is perceived as threatening or benign. A higher score will indicate a more threatening view of the illness.

Test-retest reliability was assessed with renal patients at 3-week and 6-week intervals (e.g. illness consequences $r=.70$, $p<.001$, 3-week and $r=.71$, $p<.001$, 6-week). Concurrent validity was assessed through comparison with equivalent scales of the IPQ-R in asthma, diabetes and renal patients and significant correlations were reported between items of equivalent scales (e.g. consequences, $r=.62$, $p<.001$). Discriminant validity showed significant differences between illnesses (e.g. diabetes and asthma). Predictive validity was shown with patients recovering from myocardial infarction. Illness consequences were associated with mental health functioning ($r=-.58$, $p<.001$), measured by the SF-36 and illness identity was associated with physical functioning ($r=-.50$, $p<.001$), measured by the Seattle Angina Questionnaire. The internal reliability for the overall scale in PA patients was $\alpha=.60$.

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

This scale has been widely used as a measure of health status in clinical populations, measuring symptoms of depression and anxiety (Bock, Bendstrup, Hilberg & Lokke, 2017; Peltzer & Pengpid, 2016; O'Connor et al., 2010; McLaughlin et al., 2005; It is comprised of fourteen non-somatic symptoms of depression and anxiety, rated according the degree to which these have been experienced over the past two weeks, on a 4-point Likert scale (Appendix 4.17). Total scores are calculated for the two subscales, where higher scores indicate greater levels of depression and anxiety.

Scores between 0-7 reflect scores within the normal range, scores within 8-10 indicate the presence of state depression and/or anxiety and scores above 11 reflect caseness of mood disorder. The HADS has good psychometric properties. In the original scale, HADS scores were associated with clinical ratings ($r=0.54$ for anxiety and $r=.79$ for depression). Concurrent validity was assessed with the beck depression inventory and reported correlations for anxiety ranged from .61 to .83 and for depression correlations ranged from .62 to .73 (Bjelland et al., 2002). Discriminant validity was assessed in a few studies were independence from anxiety and depression were supported (Clark & Watson, 1991; Aylard et al., 1987). Internal reliability of the measure of anxiety in the PA population was $\alpha = .87$ and for the depression scale $\alpha = .84$.

The World Health Organization Quality of Life Assessment (WHOQOL-BREF; Skevington, Lofty, O'Connell & WHOQOL group, 2004)

The 26-item version of the WHOQOL-100 scale (Skevington, 1999) has good to excellent psychometric properties of reliability and validity measuring across four domains, physical health, psychological health, social relationships and environment. Responses are rated on a 5-point Likert scale. Raw scores in each dimension are converted to transformed scores in a linear 0-100 scale. Higher scores denote improved HRQoL. It also includes two general questions that relate to life satisfaction and general quality of life. It has been employed in different areas such as medical practice, research and audit, policy making as well as assessing the effectiveness of different treatments (Gholami, Jahromi, Zarei & Dehghan, 2013; Shavro, Ezhilarasu, Augustine, Betchel & Christopher, 2012; Skevington & McCrate, 2012; Chachamovich, Trentini & Fleck, 2007; Van Heck & de Vries, 2003).

It may also be used to assess cross-cultural variation, to compare sub-groups within the same culture and to measure change across time in response to change in life circumstances. The HRQoL dimensions possessed good internal reliability for the PA population (physical health $\alpha=.68$; psychological health $\alpha=.88$; social relationships $\alpha=.69$; environment $\alpha=.81$).

6.3.5.1. Comparison of the validity scores of the WHOQOL-BREF in the PA population with the original WHOQOL-BREF scale

The psychometric properties of reliability and validity of the WHOQOL-BREF were examined in the PA population and compared with the original validity scores of the WHOQOL-BREF (Skevington, Lofty & O'connell, 2004). In the original WHOQOL-BREF study, participants were recruited from various settings, which included in-patient and outpatient healthcare facilities and well samples in different study centres (including the UK). Considering that the present thesis refers to the administration of the WHOQOL-BREF in a PA population, comparison of validity scores with the original scale is limited. Given the absence of similar methodology with the original study (Skevington, Lofty & O'connell, 2004) it was only possible to compare the reliability (cronbach's alpha) and construct validity with the original scale. The criterion for acceptable reliability in the original scale was $>.7$.

Reliability

A reliability analysis was carried out on the four dimensions of the WHOQOL-BREF. For the physical dimension (7 items), the Cronbach's Alpha reached marginal reliability ($\alpha=.68$). Most items present in this scale were worthy of retention, resulting in a decrease in reliability if deleted.

The one exception to this was item 16 (sleep), which would increase the reliability to $\alpha=.86$. The psychological dimension scale (8 items) reached good levels of reliability ($\alpha=.88$) and all items were worthy of retention. The dimension of social relationships ($\alpha=.69$) and environment ($\alpha=.61$) reached marginal reliability scores. These reliability scores are partly consistent with the scores found for the original WHOQOL-BREF data set where only one item (negative feelings) was considered to have low reliability ($\alpha=.56$).

At this point, reliability of the dimensions of psychological health and environment in the PA population have similar levels of reliability in comparison with the total population used to test the WHOQOL-BREF scale (physical health $\alpha=.82$; psychological health $\alpha=.81$; social relationships $\alpha=.68$; environment $\alpha=.80$). Reliability scores are also similar with the ones reported for the UK centre (physical health $\alpha=.87$; psychological health $\alpha=.74$; social relationships $\alpha=.55$ and environment $\alpha=.74$).

Construct validity

Construct validity was assessed to investigate if items were clearly identified with the intended domain. Analysis of the correlations concerning the scores in the PA population showed that eleven items had strong correlations ($>.50$) with domains other than their intended domain (Skevington, Lofty & O'Connell, 2004).

These items were part of the psychological dimension (enjoyment, meaning, concentration, personal satisfaction and negative feelings) strongly correlating with items from the physical, environmental and social dimensions. Items from the physical dimension (energy, activities of daily living and work) strongly correlated with the psychological and environmental dimensions. Items from the social dimension (personal relationships) strongly correlated with items from the psychological dimension. Lastly, items from the environment dimension (safety and leisure) strongly correlated with the physical, psychological and environmental domains. Whilst cross-domain correlations may be expected, the majority of items did not correlate more strongly with items from other domains. Only occasionally, the item of safety was more strongly correlated with the physical (energy and activities of daily living) and psychological domains (concentration).

In the original WHOQOL-BREF data set, seven items had strong correlations with other domains (Skevington, Lofty & O'Connell, 2004). These items were reflected in the physical domain (energy, activities of daily living and work), strongly correlating with the psychological domain. The self-esteem item from the psychological dimension correlated highly with all of the other dimensions. Other items included positive feelings (psychological) relationships (social relationships) and safety (environment).

In the PA population, item-domain correlations ranged from 0.37 (treatment) to 0.74 (activities of daily living) for the physical domain, to 0.59 (body appearance) to 0.81 (personal satisfaction) for the psychological domain, to 0.47 (transport) to 0.62 (safety) for the environmental domain, to 0.47 (friendship support) to 0.54 (personal relationships) for the social relationships domain. Pearson correlations (2-tailed) were strong and statistically significant ($p < .001$), ranging from 0.42 (physical vs. social) to .78 (psychological vs. environmental). These results are somewhat similar to the item-domain correlations for the items of activities of daily living and personal relationships in the original WHOQOL-BREF data set. Pearson correlations were strong and statistically significant ($p < .001$), ranging from 0.46 (physical vs. social) to .67 (physical vs. psychological).

Considering the initial comparison between the validity scores from the WHOQOL-BREF in the PA population with scores derived from the original data set, it appears that the instrument performs well in terms of reliability and construct validity. However, as pointed out by the authors of the WHOQOL-BREF (Skevington, Lofty & O'Connell, 2004) item identification would require further attention as specific items (e.g. safety, more strongly associated with the psychological domain) could be improved to reflect their intended domain (environment). Alternative explanations may relate to a change in respondents' environment.

6.3.6 Procedure

Two surgeries from different areas within the ABMU health board were purposively selected for participation in the present study. Both GP surgeries are engaged with the primary care research incentive scheme (PiCRIS), an initiative developed to offer support, mentorship and funding to general practices across Wales to become research active and embed research activity in their daily practice. Patients who met the inclusion criteria were invited to participate in the study through their local GP surgeries. Participants were sent out a postal survey with a covering letter from their attending surgeries explaining the reason why they were being contacted, the patient information sheet (PIS; Appendix 4.7) and consent form (Appendix 4.8) explaining the study aims and procedures. It was made plain to participants that they had time to think whether to participate in the research study (PIS). The principal investigator provided participants with her contact (PIS) in case they had any issues completing the survey. Participants were required to complete the survey and return it back to the surgery in a pre-paid envelope. Reminders to follow-up from voluntary participation were sent out approximately 3 weeks after the initial contact was made. The practice nurse also raised awareness of the study when patients attended their surgeries for scheduled injections. This included asking patients if they were aware that the study was taking place and giving them a copy of the survey in case they were interested in participating. The data collection period started in October 2016 and ended in January 2017. The researcher collected the surveys at the end of the data collection period. To ensure that a broader population was targeted, the survey was also posted online (via Survey Monkey). Participants were recruited via Social Media websites (PAS and subsidiary groups, the University of South Wales intranet and Facebook pages).

The online survey, information and consent forms were identical to the postal survey administered to NHS patients. The data collection period started in January 2017 and ended in March 2017. Participants were informed that a summary of study results would be made available once all the research related tasks were completed.

6.3.7 Instrument development

Meaningful items within the validated measures served as basis for the HRQoL prototype (PA-HRQoL). Additional items were generated from findings from the pilot studies in the present thesis, and a comprehensive literature review to ensure relevant items captured the perspective of PA sufferers. The draft measure includes 43 items measured across seven dimensions (physical functioning; psychological health; illness management behaviours; illness controllability and support; maladaptive coping; illness understanding and adjustment; distraction).

Thirty-nine items were generated through Principal Component Analysis, and four items relate to the experience of specific symptoms (poor concentration, pins and needles, numbness of extremities, and shortness of breath) that emerged from existing PA literature and qualitative accounts of PA sufferers, outlined in the present thesis (study 1, 2 and 3). These additional symptoms were integrated within the first dimension (physical functioning) due to the apparent similarity with items in the same dimension. Where appropriate, and kept to a minimum, item phrasing was reworded to ensure consistency with the response categories (Gu, Cavanagh, Baer & Strauss, 2017; Patrick et al., 2011). This included changing items worded as questions to statements and removing frequency terms (e.g. 'how much').

Instructions for completing the questionnaire were provided and responses are measured in a 5-point Likert scale format (no, not at all; a little; moderately; very much; extremely), Miller (1956).

A 4-week time frame was selected (WHO, 1996) in line with many well-established HRQoL measures, such as the 36-Item Short Form Survey Instrument (SF-36; McHorney, Ware, Lu & Sherbourne, 1994) and the WHOQOL-BREF (Skevington, Lofty, O'Connell & WHOQOL group, 2004). Validation of the PA-HRQoL instrument is not part of the present thesis and it is yet to be established. Content validity will be assessed through the patient perspective, in terms of providing critical feedback once the instrument is piloted, to establish acceptability and practicality (Patrick et al., 2011).

6.4 Results

The aims of the present study are to investigate the best predictors of overall quality of life and to develop a patient-centred outcome measure for the identification of health-related quality of life in patients suffering with PA. Prior to addressing these aims, descriptive statistics were computed for the sample.

6.4.1 Descriptive analyses

Information recorded included demographics and clinical data. Information recorded included ethnic background, source of recruitment, marital status, employment, affiliation to support groups, type of diagnosis, family history, time since diagnosis, treatment related information and co-morbidities. Psychological measures will include illness representations; health status; locus of control; somatic focus; coping strategies; quality of life. Data was checked for normality prior to computing descriptive analyses. Patients' demographics and clinical characteristics were summarised by frequencies and percentages, and means and standard deviations, where appropriate.

6.4.1.1 Normal distribution

The Shapiro-Wilk test was employed as numerical means of assessing normality for the variables of 'age and 'gender'. This test is appropriate to use in small sample sizes (Field, 2009).

The observed value of the Shapiro-Wilk ($W=0.976$) and the exact probability of the outcome was not statistically significant ($p=0.528$).

Therefore, the observed distribution for the variable 'age' in males fits the normal distribution, with skewness of -0.220 ($SE=0.37$) and Kurtosis of -0.77 ($SE=0.32$).

The observed value of the Shapiro-Wilk ($W=0.987$, $p= 0.191$), with skewness of 1.41 ($SE=0.20$) and Kurtosis of -0.511 ($SE=0.40$). The observed distribution for the variable 'age' in females fits the normal distribution.

Normality was further explored for the remaining variables in the study to investigate potential data skewness. The data deviates from normality for the other recorded variables. The sample ($N=184$; 144 females, 40 males; $M = 56.2$, $SD=16.1$) included patients from two GP surgeries in the area of Bridgend (37%) and Port Talbot (17%) and patients recruited online (46%), from various areas in the UK. Tables 6.4.1.2 display the survey response rates.

Table 6.4.1.2

Response rates from GP surgeries

Recruitment	Surveys sent out	Returned surveys	Agreed to participate	Declined participation	No response	Response rate	Total(n)
GP surgery Bridgend	220	121	68	53	99	55%	68
GP surgery Port-Talbot	206	56	32	24	151	27%	32
Total	426	177	100	77	250	41%	100

The table above highlights that the study achieved an overall response rate of 41%, regarding the recruitment of patients through GP surgeries. In light of this, sample representativeness may be questioned (Draugalis, Coons & Plaza, 2008; Fincham, 2008).

6.4.2 Characteristics of the population

Patient data indicated that the majority of the population was White British (97.3%). Only a small proportion of the population were from any other background (2.7%). The sample included patients from two GP surgeries in the area of Bridgend (37%) and Port Talbot (17%). It also included patients recruited online, from various areas in the UK (46%). The majority of the sample was married (57.1%) and the highest level of education recorded was higher education (44.7%) followed by GCSE/O level (24.7%) and further education (21.2%). Employment information indicated that the largest single group was employed (44%). In 36.8% of the cases, individuals were retired. Affiliation to support groups was recorded for 38% of the cases (n=69), mainly including the PAS.

Eighty-four individuals (46%) received the diagnosis of B₁₂ deficiency and one-hundred individuals reported receiving a PA diagnosis (54%). These diagnoses were delivered by their GPs in the majority of the cases (84%). Family history of PA was recorded in 30.4% of the cases, compared to 46.2% of the cases where there was no family history and in 23.4% of the cases, individuals were not sure. Time since diagnosis varied in the population, from newly diagnosed to 50 years since diagnosis, the most frequent being one year (18.5%). Treatment was administered every 3 months for 63.2% of the cases, followed by every 2 months (12.6%) and every month (6.6%). Treatment request was recorded for 50.5% of the population as compared to 49.5% who did not request more frequent treatment. Requests were refused for the large majority (54%). In 39% of the cases, GP's agreed to change the frequency of B₁₂ treatment.

Other outcomes included pending decisions (3.5%) or receiving additional treatment on occasion (3.5%). B₁₂ additional treatment was recorded for 32% of the cases and mainly included purchasing over-the-counter injections.

A small proportion of the population reported having their treatment suspended (13%) and self-injecting (13%). 55% of the population confirmed being diagnosed with other chronic conditions, mainly conditions related to the endocrine system, musculoskeletal system and connective tissue, and gastrointestinal system.

6.4.3 Findings for the psychological measures included in the current study

Coping strategies

Table 6.4.3.1

Means and standard deviations of the measure of coping strategies administered to B₁₂/PA deficiency patients

Variable	M	SD	Range	N
BC self-distraction	3.70	1.92	2-8	179
BC active coping	4.39	2.27	2-8	179
BC denial	2.70	1.45	2-8	179
BC substance use	2.54	1.37	2-8	179
BC emotional support	3.48	1.79	2-8	179
BC instrumental support	3.72	1.85	2-8	179
BC behavioural disengagement	2.88	1.34	2-8	179
BC venting	3.45	1.72	2-8	179
BC positive reframing	3.31	1.60	2-8	179
BC planning	4.34	2.21	2-8	179
BC humour	3.21	1.73	2-8	179
BC acceptance	5.67	2.19	1-8	179
BC religion	2.51	1.24	1-8	179
BC self-blame	3.12	1.70	2-8	179

Note: M= mean; SD= standard deviation; N= number of participants.

The table shows the variables that represent coping strategies, higher mean scores represent proactive ways of coping, including active coping, planning and acceptance, compared to less proactive strategies.

Table 6.4.3.2

Means and standard deviations of the measure of multidimensional health locus of control administered to B₁₂/PA deficiency patients

Variable	M	SD	Range	N
MHLC internal	22.08	5.81	2-36	182
MHLC chance	18.68	6.18	5-33	182
MHLC powerful others	17.06	6.80	5-36	182

Note: M= mean; SD= standard deviation; N= number of participants.

The table suggests that individuals perceived having higher an internal locus of control in dealing with their illness in comparison to chance or powerful others.

Table 6.4.3.3

Means and standard deviations of the measure of somatic focus administered to B₁₂/PA deficiency patients

Variable	M	SD	Range	N
PHQ-somatic focus	13.20	7.54	0-71	182

Note: M= mean; SD= standard deviation; N= number of participants.

The table shows that somatisation appears to fall within moderate levels for this population (≥ 10).

Table 6.4.3.4

Means and standard deviations of the measure of illness representations administered to B₁₂/PA deficiency patients

Variable	M	SD	Range	N
BIPQ total	42.49	13.20	5-72	184
BIPQ consequences	5.67	3.09	0-10	184
BIPQ timeline	9.47	1.59	0-10	181
BIPQ treatment control	7.53	2.51	0-10	183
BIPQ personal control	4.16	3.15	0-10	183
BIPQ identity	6.38	2.85	0-10	184
BIPQ coherence	6.41	3.33	0-10	184
BIPQ concern	6.09	3.28	0-10	184
BIPQ emotional representation	3.52	4.16	0-10	184

Note: M= mean; SD= standard deviation; N= number of participants.

The table shows that illness threat appears to fall within moderate levels for this population. Individuals seemed to have a very good understanding of illness chronicity (timeline) and believed that treatment would be beneficial to their condition. Individuals seemed to experience symptoms (identity) and worry about their illness (concern) to a moderate degree. Results also suggest that individuals may have a reasonable illness understanding (coherence).

Table 6.4.3.5

Means and standard deviations of the measure of health status administered to B₁₂/PA deficiency patients

Variable	M	SD	Range	N
HADS anxiety	8.68	5.23	0-21	184
HADS depression	7.50	4.68	0-19	184

Note: M= mean; SD= standard deviation; N= number of participants.

Psychological distress measures indicate the presence of anxiety state (8-10) in this population and levels of depression slightly fall above the normal range (0-7).

Table 6.4.3.6***Means and standard deviations of the measure of health-related quality of life administered to B₁₂/PA deficiency patients***

Variable	M	SD	Range	N
Perceived QOL	3.51	1.05	1-5	183
Perceived life satisfaction	2.67	1.10	1-5	182
WHOQOL-BREF physical health	48.55	14.03	6-81	183
WHOQOL-BREF psychological health	52.88	17.41	0-88	183
WHOQOL-BREF social relationships	56.67	25.14	0-100	182
WHOQOL-BREF environment	68.01	19.24	19-100	183

Note: M= mean; SD= standard deviation; N= number of participants.

Perceived quality of life seems to be neither poor/nor good for most of the individuals. Results indicate that most of the individuals seem to be slightly dissatisfied with their lives. Regarding the dimensions of HRQoL, results seem to point that social relationships and environment contributed to a better HRQoL.

Findings from the current study suggest acceptance and planning as ways of dealing with one's illness. Literature has previously identified these strategies as adaptive (Uchmanowicz, Jankowska-Polanska, Motowidlo, Uchmanowicz & Chabowski, 2015; Kostova, Caiata-Zufferey & Schulz, 2014; Pierobon, Giardini, Callegari & Majani, 2011; Büssing, Ostermann, Neugebauer and Heusser, 2010). The engagement in coping styles that have been suggested as less adaptive such as self-blame, venting and behavioural disengagement have also been highlighted in the currently study and documented in previous research (Cameron & Wally, 2014; Kaltsouda et al., 2011; Büssing, Ostermann, Neugebauer & Peter Heusser, 2010).

Patients seemed to have a reasonable understanding regarding the chronicity of their illness. However, the majority seemed to experience symptoms to a moderate degree and express concern toward their condition. Most individuals seemed to believe they could control their illness to a moderate extent. These findings are similar with studies conducted with other populations (Clarke, Yates, Smith & Chilcot, 2016; Moss-Morris et al., 2002). The levels of depression and somatisation (Patel, Morgan, Bercik & Ford, 2015) seemed to be moderate for this population. However, it also indicated the presence of state anxiety as opposed to trait anxiety. Psychological distress seems to be a common occurrence in patients experiencing chronic illness (Tselebis et al., 2016; Clarke & Currie, 2009). Perceptions of better social relationships and environmental health seemed to be the most meaningful aspects of HRQoL in this population.

6.5 Aim 1

To investigate the best predictors of health-related quality of life.

This aim will be addressed by computing multiple regression analyses for the four dimensions of health-related quality of life (physical health, psychological health, social relationships and environment). The WHOQOL-BREF was used as a measure of adjustment, reflecting the HRQoL of PA sufferers. Prior to conducting multiple regression analyses, investigations were carried out to check for outliers, collinearity of data, independent errors, homocedascity and linearity of data, and non-zero variances. Correlation coefficients between the variables were determined prior to conducting multiple regression analyses (Field, 2009). Only items with acceptable levels of correlations ($r > .3$) and items that did not correlate too highly ($r < .9$) were included in the multiple regression analyses. The variables that satisfied the above criteria derived from the Brief-Cope (venting, behaviour disengagement; emotional support; denial and self-blame) HADS (anxiety and depression) and Brief-IPQ (consequences, treatment, concern, identity, emotional representation) scales.

6.5.1 WHOQOL physical health

An analysis of standard residuals showed that the data contained one outlier. This was removed to reflect no outliers (*Std.Residual Min* = -2.87, *Std Residual Max* = 2.79). Tests to check if the data met the assumption of collinearity indicated that multicollinearity was not a concern. The data met the assumption of independent errors (*Durbin-Watson value* = 2.08). The scatterplot of standardised residuals showed that the data met the assumptions of homogeneity of variance and linearity. The data also met the assumption of non-zero variances.

In order to assess the contributions of the variables in predicting the physical health dimension of health-related quality of life, a forced entry multiple regression was performed, previously reported as an appropriate method for theory testing (Studenmund & Cassidy, 1987). The results of this analysis indicated that all the variables that represent coping, illness representations, anxiety and depression, explained a reasonable amount of the variance in physical health to a statistically significant level ($F(9,166) = 10.02, p < .05, R^2 = .35, R^2_{adjusted} = .31$). Table 6.5.1.1. displays the regression coefficients for each individual variable.

Table 6.5.1.1

Regression coefficients of each predictor using physical health as the criterion variable (n=176)

Predictor	Beta	t	Sig	Tolerance	VIF
BIPQ consequences	-.309	-2.423	P<.05	.332	3.014
HADS depression	-.353	-3.259	P<.05	.332	3.016

Results from the analysis show that from all the predictors in the study, only illness consequences ($r = -.467, p < .01$) and depression ($r = -.531, p < .01$) made a significant individual contribution in predicting physical health.

6.5.2 WHOQOL Psychological health

An analysis of standard residuals showed that the data contained one outlier. This was removed to reflect no outliers (*Std. Residual Min* = -2.46, *Std Residual Max* = 2.44). Tests to check if the data met the assumption of collinearity indicated that multicollinearity was not a concern.

The data met the assumption of independent errors (*Durbin-Watson value* =2.00). The scatterplot of standardised residuals showed that the data met the assumptions of homogeneity of variance and linearity. The data also met the assumption of non-zero variances.

In order to assess the contributions of the variables in predicting the psychological health dimension of health-related quality of life, a forced entry multiple regression was performed. The results of this analysis indicated that the variables that represent coping, illness representations, anxiety and depression explained an acceptable amount of the variance in psychological health to a statistically significant level ($F(12,163) = 18.31, p < .05, R^2 = .57, R^2_{adjusted} = .54$). Table 6.5.2.1 displays the regression coefficients for each individual variable.

Table 6.5.2.1

Regression coefficients of each predictor using psychological health as the criterion variable (n=176)

Predictor	Beta	t	Sig	Tolerance	VIF
HADS depression	-.575	-6.381	P<.05	.326	3.064
BIPQ identity	.246	2.386	P<.05	.272	3.682
BIPQ treatment control	.197	3.601	P<.05	.877	1.140
BIPQ consequences	-2.34	-2.189	P<.05	.241	4.144

Results from the analysis show that from all the predictors in the study, treatment control ($r=.360, p<.01$), illness identity ($r=-.349, p<.01$), illness consequences ($r=-.471, p<.01$), and depression ($r=-.680, p<.01$) made statistically significant contributions in explaining psychological health.

6.5.3 WHOQOL social relationships

An analysis of standard residuals showed that the data contained no outliers (*Std. Residual Min*=-2.90, *Std Residual Max* = 2.92). Tests to check if the data met the assumption of collinearity indicated that multicollinearity was not a concern. The data met the assumption of independent errors (*Durbin-Watson value* =2.08). The scatterplot of standardised residuals showed that the data met the assumptions of homogeneity of variance and linearity. The data also met the assumption of non-zero variances.

In order to assess the contributions of the variables in predicting the dimension of social relationships of health-related quality of life, a forced entry multiple regression was performed. The results of this analysis indicated that the variables that represent coping, illness representations, anxiety and depression, explained an acceptable amount of the variance in social relationships to a statistically significant level ($F(5,171) = 10.08, p < .05, R^2 = .22, R^2_{adjusted} = .20$). Table 6.5.3.1 displays the regression coefficient for the variable that emerged as the only significant predictor of social relationships.

Table 6.5.3.1

Regression coefficients of each predictor using social relationships as the criterion variable (n=176)

Predictor	Beta	t	Sig	Tolerance	VIF
HADS depression	-.312	-2.881	P<.05	.384	2.604

Results from the analysis show that from all the predictors in the study, only depression ($r = -0.57, p < .01$) made a significant contribution in explaining the HRQoL dimension of social relationships.

6.5.4 WHOQOL environment

An analysis of standard residuals showed that the data contained three outliers. These were removed to reflect no outliers (*Std.Residual Min*=-2.87, *Std Residual Max* = 2.27). Tests to check if the data met the assumption of collinearity indicated that multicollinearity was not a concern. The data met the assumption of independent errors (*Durbin-Watson value* =1.93). The scatterplot of standardised residuals showed that the data met the assumptions of homogeneity of variance and linearity. The data also met the assumption of non-zero variances.

In order to assess the contributions of the variables in predicting the environment dimension of health-related quality of life, a forced entry multiple regression was performed. The results of this analysis indicated that all the variables that represent coping, illness representations, somatic focus, anxiety and depression explained an acceptable amount of the variance in environment to a statistically significant level ($F(10,164) = 15.99$, $p < .05$, $R^2 = .49$, $R^2_{adjusted} = .46$). Table 6.6.1 displays the regression coefficients for each individual variable.

Table 6.5.4.1

Regression coefficients for each predictor using environment as the predictor variable (n=175)

Predictor	Beta	t	Sig	Tolerance	VIF
HADS anxiety	-.321	-3.632	P<.05	.396	2.528
BIPQ identity	.203	1.820	P<.05	.231	4.320
BIPQ consequences	-.57	-3.088	P<.05	.486	2.056

Results from the analysis show that from all the predictors in the study, only anxiety ($r=-.563$, $p<.01$), illness identity ($r=-.352$ $p<.01$) and illness consequences ($r=-.471$, $p<.01$) made significant contributions in explaining the environment dimension of health-related quality of life.

Outcomes from the multiple regression analyses were presented according to the best predictors in each HRQoL dimension (physical health, psychological health, social relationships and environmental health). Findings suggested that the best predictors of physical health were illness consequences and depression. The best predictors of psychological health were illness perceptions that relate to illness identity, illness consequences, treatment control and depression. Social relationships were better explained by health status (depression). The variables that were better at explaining environmental health were anxiety and illness perceptions (identity and consequences). Results from the present study have significant implications in terms of highlighting the importance of psychosocial factors in the management of B₁₂ deficiency. Studies that may provide support for the current findings have explored the relationship between illness perceptions, psychological distress and different facets of health-related quality of life in patients presenting with various chronic conditions. Faller and colleagues (2009) investigated the simultaneous influence of heart failure severity and comorbid depression on the physical function and psychological domains of HRQoL. This study recruited 206 outpatients suffering from chronic heart failure. Depression was measured using the patient health questionnaire (PHQ-9) and HRQoL was measured using a condition-specific instrument, the Kansas City cardiomyopathy questionnaire.

The New York heart association functional class ratings assessed the impact of symptom severity on activities of daily living. The aim of this study was to examine whether both HRQoL dimensions were affected by comorbid depression considering symptom severity. Results from this study suggested that depression had an impact on both physical and psychological HRQoL domains. However, the severity of patient's symptoms only had an impact on the physical HRQoL domain. These findings may highlight the significance of illness perceptions, since patients that experience depression may appraise their health status in a more negative way.

Another study investigating health-related quality of life and disability in patients with chronic obstructive pulmonary disorder has found that psychological factors such as depression and perceived illness threat were important predictors of low HRQoL and high disability in these patients. However, in these patients, co-morbid somatic symptoms were the most important predictors of physical health (Mewes, Rief, Klenn, Ried & Stenzel, 2015). While somatisation did not emerge as a significant predictor of HRQoL in the PA population, it had low negative associations with all dimensions of HRQoL. A longitudinal cohort study investigated the predictors of health-related quality of life in people with chronic conditions presenting with multimorbidity, over a 12-month period. The variables assessed included demographics, disease, intervention factors and psychosocial factors. Results suggested that the most significant predictors included the impact of illness on activities of daily living, the number of co-morbidities, health functioning and psychological distress (Tyack, Frakes, Barnett, Cornwell, Kuys & McPhail, 2016).

A systematic review of 11 independent published studies showed a significant association between depression and subsequent physical aspects of HRQoL in patients suffering with coronary heart disease. This association was reported independently of the severity of the condition and impairment of physical HRQoL at baseline. Depression was mostly assessed using the HADS and the Beck Depression Inventory and HRQoL was mostly assessed using generic measures such as the SF-36. Results suggested that nine of the studies reported a strong association between depression and physical HRQoL. These findings may suggest that individuals may negatively appraise physical health due to lack of motivation and experienced fatigue (Dickens, Cherrington & McGowan, 2012). The relationship between illness perceptions and quality of life was explored in a sample of 100 patients suffering with chronic obstructive pulmonary disorder. This study indicated that the perception of negative illness consequences and more physical complaints were associated with poorer HRQoL (Tiemensma, Gaab, Voorhaar, Asijee & Kaptein, 2016).

Another study looking at health-related quality of life predictors in patients with rheumatoid arthritis has found that pain, functional disability and depression were the main predictors of HRQoL (Wan et al., 2016). In other studies, negative affect has been inversely associated with all dimensions of quality of life (Vilhena et al., 2014; Graydon, Bubela, Irvine & Vincent, 1995).

Literature has suggested psychological factors as important predictors of outcome, influencing one's illness and treatment control, having significant implications in terms of managing disease severity (Rochelle & Fidler, 2012; Engstrom et al., 2001).

The fact that treatment control emerged as a significant predictor of psychological health is supported by existing literature suggesting that perceptions that treatment will benefit one's condition may be associated with improved quality of life (Rochelle & Fidler, 2012). Alternatively, the perceived experience of severe symptoms has also been linked to the experience of psychological distress subsequently affecting one's adjustment. Morgan, Villiers-Tuthill, Barker and McGee (2014) have documented the contribution of illness perceptions to depression and anxiety indices in patients experiencing heart failure. Although patients seemed to have a good illness understanding and perceived treatment to be effective, they perceived greater illness consequences and negative emotional responses. These negative influences on one's psychological well-being may contribute to a reduced health-related quality of life. Alternatively, patients did not attribute most of their symptoms to their condition. The same may not be suggested for PA patients, which attributed a somewhat higher proportion of symptoms to their illness identity (mean score=6.38). This may also be related to illness co-morbidity in the PA population (55%).

A study by Le Grande and colleagues (2012) has examined different illness perception profiles in cardiac patients and its association with quality of life and depression. Illness perceptions were measured using the BIPQ, depression was assessed using the Beck Depression Inventory II and quality of life was measured by the MacNew HRQoL instrument, designed for cardiac patients. Findings from this study demonstrated that cardiac patients developed a structured pattern of beliefs about their existing condition leading to different outcomes. In example, patients identified as being highly focused on the consequences of their condition as well as perceiving little control over the same presented with high levels of depression and poor HRQoL.

Alternatively, patients who felt in control over their illness perceiving lower illness consequences reported experiencing mild depression and improved HRQoL (Le Grande et al., 2012).

Depression emerged as the only significant predictor of social relationships HRQoL. The functional limitations resulting from experiencing chronic illness may result in increased psychological distress. Subsequently, this may affect one's ability to form meaningful relationships and benefit from social support (Turner, 2000). The predictive value of social support on HRQoL has been investigated in conditions such as multiple sclerosis. In a cross-sectional design and a sample of 150 patients, social support was assessed using the medical outcomes study social support survey (emotional and informational support, tangible, affectionate, positive social interaction) and quality of life was assessed using the health status questionnaire (SF-36v2). Regression analyses indicated that social support was positively associated with HRQoL. However, in this study, the dimension of emotional support emerged as a significant predictor for all dimensions of HRQoL. These findings highlight the importance of social relationships in illness adjustment (Costa, Sá & Calheiros, 2011).

The investigation of the relationship between individual dimensions of illness representations and anxiety provides an insight into the dimension of environmental HRQoL. Research has documented the reported negative effects of type 2 diabetes such as the experience of symptoms and increased anxiety and its relationship with poor environmental HRQoL, where patients felt unsafe and perceived lack of facilities to exercise (Chew, Mohd-Sidik & Shariff-Ghazali, 2015). Similar findings have been documented in other conditions such as rheumatoid arthritis (Wan et al., 2016; Iversen, Scanlon, Frits, Shadick & Sharby, 2015).

6.6. Aim 2

To develop a patient-centred outcome measure for the identification and management of health-related quality of life in patients suffering with PA. To address this aim, factor analysis (PCA) was performed to identify factors in the data that form the basis of the patient-centred outcome tool. Individual item scores were normalised prior to conducting PCA.

6.6.1 Principal Components Analysis

In total, there were six scales. These scales measured illness perceptions (BRIEF-IPQ), anxiety and depression (HADS), coping strategies (Brief-Cope), somatic focus (PHQ-15), locus of control (MHLOC) and health-related quality of life (WHOQOL-BREF). Overall, the scales consisted of 107 items. Negatively worded items were reverse-coded prior to analysis. Prior to conducting exploratory factor analysis and to ensure there were no issues with data multicollinearity, the correlation matrix was examined to check the pattern of relationships between the items. Items with low correlations ($r < .3$), items that did not correlate with any other variables or correlated highly ($r > .9$) with other variables, were eliminated from the analysis (Field, 2009). Subsequently, measures of sampling adequacy (Kaiser-Meyer-Olkin; KMO) were examined to check that the patterns of the correlations yielded reliable factors. As per recommendation (Kaiser, 1974) any items with values below the acceptable level of .5 were removed. This was the case for forty-eight items. A principal components analysis (PCA) was conducted on the remaining 59 items with orthogonal rotation (varimax), as suggested in case factors are expected to be independent (Field, 2009).

The KMO measure indicated a high value (Hutcheson & Sofroniou, 1999), verifying the sampling adequacy for the analysis (KMO=.88). All KMO values for individual items were above .5. Bartlett's test of sphericity, which tests the overall significance of correlations between all the variables, was highly significant ($\chi^2 (1711) = 6025.95, p <.001$), indicating that factor analysis is appropriate for the data. An initial analysis was conducted to obtain eigenvalues for each data item. Thirteen factors were initially obtained, meeting Kaiser's criterion, eigenvalues greater than 1. However, four of these had no substantial loadings (only two items or less). An examination of the factor structure and the convergence of the scree plot, as recommended to aid decisions regarding the number of factors to retain (Costello & Osborne, 2005), justified running the analysis looking at a 9-factor solution and subsequently an 8-factor solution. Both failed to converge in a significant number of iterations. Subsequently, a 7-factor solution was carried out and it seemed to have better described the data, producing cleaner loadings across the factors, with a total variance of 56.37%.

These factors loaded at higher than .4. This suppression value was chosen to assist with the interpretation of the factor structure (Field, 2009). Items in the factors were retained on the basis of having strong factor loadings (.4 or greater) and at least .2 difference between the highest loading and loadings onto other factors (Davies et al., 2000; James et al., 2004, as cited by West & Roderique-davies, 2008), since the goal of FA is to explain the variance between the common factors (Child, 2006). Factors were also retained if they included a minimum of three items per factor, to ensure that factors were well-determined (Field, 2009).

Items were removed if they didn't appear to make significant contributions to the overall factor, such as not being theoretically related to the highest loading items in a specific factor. Table 6.6.1.1 .presents the factor structure and loadings of items to specific factors.

Table 6.6.1.1

Summary of the results from exploratory factor analysis

Factor	Eigenvalue	% of variance
1	18.59	30.47
2	4.48	7.35
3	2.60	4.26
4	2.50	4.10
5	1.87	3.07
6	1.77	2.90
7	1.64	2.70

Table 6. 6.1.1 shows the 7 factors that were identified and retained in the final analysis. These factors possess moderate to high reliabilities with Cronbach's α values ranging from .46 to .82. Factor 1 consists of seven items and represents physical functioning. Factor 2 comprises of ten items and suggests the impact of illness on psychological health. Factor 3 consists of seven items and outlines different ways of dealing with PA. Factor 4 consists of three items and relates to illness related control and support. Factor 5 includes 3 items and represents maladaptive coping. Factor 6 consists of 5 items and suggests illness understanding and adjustment. Factor 7 comprises of four items associated with distraction strategies.

Table 6.6.1.2

Summary of exploratory factor analysis results from the HRQOL, Somatic symptoms, Brief-IPQ and HADS scales

Item	Factor Loadings						
	Physical functioning	illness impact on psychological health	Illness management behaviours	Illness controllability and support	Maladaptive coping	illness understanding and adjustment	Distraction
I feel as I have slowed down	.69						
During the past 4 weeks, how much have you been bothered with feeling tired or having little energy?	.56						
During the past 4 weeks, how much have you been bothered with chest pain?	.56						
How much does your illness affect your life?	.55						
During the past 4 weeks, how much have you been bothered with constipation, loose bowels or diarrhoea?	.51						
I look forward with enjoyment to things	.51						
During the past 4 weeks, how much have you been bothered with trouble falling or staying asleep or sleeping too much?	.49						
I get sudden feelings of panic		.80					
I get a sort of frightened feeling like 'butterflies' in the stomach		.79					
I get sort of a frightened feeling as if something awful is about to happen		.77					
Worrying thoughts go through my mind		.69					
I feel tense or 'wound up'		.67					
How often do you have negative feelings such as blue mood, despair, anxiety, depression?		-.60					
I have been giving up trying to deal with it		.47					
I can laugh and see the funny side of things		.45					
I can enjoy a good book or radio or TV programme		.44					
I have been getting help or advice from other people		.41					
I have been getting emotional support from others			.73				
I have been concentrating my efforts on doing something about the situation I am in			.70				

Item	Factor Loadings						
	Physical functioning	illness impact on psychological health	Illness management behaviours	Illness controllability and support	Maladaptive coping	illness understanding and adjustment	Distraction
I have been getting comfort and understanding from someone			.67				
I have been thinking hard about what steps to take			.67				
I have been trying to get advice or help from other people about what to do			.62				
I have been expressing my negative feelings			.45				
I have been making fun of the situation			.41				
How much control you feel you have over your illness?				.51			
How much do you think your treatment can help your illness?				.50			
How satisfied are you with your personal relationships?				.43			
I have been using alcohol or other drugs to help me get through it					.61		
I have been saying things to let my negative feelings escape					.57		
I have been refusing to believe that it has happened					.56		
I have been learning to live with it						.67	
I have been accepting the reality of the fact that it has happened						.62	
How available to you is the information you need in your day-to day-life?						.44	
How well do you feel you understand your illness?						.42	
How healthy is your physical environment?						.41	
I have been trying to find comfort in my religion or spiritual beliefs							.72
I have been praying or meditating							.71
I have been doing something to think about it less, such as going to movies, watching TV reading ,daydreaming, sleeping, or shopping							.59
I have been turning to work or other activities to take my mind off things							.53
Eigenvalues	18.59	4.48	2.60	2.50	1.87	1.77	1.64
% of variance	30.47	7.35	4.26	4.10	3.07	2.90	2.70
A	.82	.81	.86	.46	.66	.63	.70

Note: Factor loadings above .4 appear in boldface

Factor 1: Physical functioning

This factor is composed of seven items and reflects physical functioning. This factor combines two items from the HADS measure that relate to the experience of depression, illness consequences and four somatic symptoms included in the PHQ-15 (tiredness, chest pain, bowel and sleeping problems). Existing literature supporting this factor has established the association between depression and illness consequences in determining health-related quality of life in patients suffering with rheumatoid arthritis. In this way, worries about the consequences of disease were important correlates of physical dimension of HRQoL (Hyphantis et al., 2013). Another study has found that patients' perceived illness consequences and emotional representations mediated symptom severity and overall health-related quality of life in patients with irritable bowel syndrome (De Gutch, 2015). The present study may partly support the presence of moderate somatisation for the majority of the population. Although PA sufferers don't perceive some of their symptoms as psychosomatic, pilot work has previously reported their symptoms being labelled as psychosomatic, by health professionals. The experience of four additional symptoms that significantly emerged from pilot work and PA research (Hooper, Hudson, Porter & McCaddon, 2014; Springhouse, 2005; Sethi, Robilotti & Sadan, 2004) were included in this factor, due to the similarity with the items included in this factor. These items were numbness, pins and needles, poor concentration and shortness of breath. The first two symptoms may indicate neurological abnormalities, resulting from the delayed diagnosis of PAB₁₂ deficiency, an important element that has emerged from narrative accounts of PA sufferers. Thus, this factor comprises of eleven items.

Factor 2: Illness impact on psychological health

Factor 2 represents the impact of pernicious anaemia on psychological health. This factor comprises of ten items and combines the emotional representation of illness with five symptoms of anxiety, two items that relate to depression, one item that relates to the experience of negative mood (psychological HRQoL), one item that reflects behaviour disengagement and one item that relates to instrumental support. Previous studies have documented the impact of chronic illness in one's psychological health. This includes the experience of depression, anxiety and response to illness, being detrimental to one's HRQoL (Finnegan-John & Thomas, 2013; Major & Glass, 2013). Behaviour disengagement has been associated with more depressive symptoms (Kaltsouda et al., 2011) and poorer HRQoL (Cartwright, Endean & Porter, 2009). Research in a population suffering with diabetes has suggested the negative association between experiencing anxiety and seeking instrumental support (Tuncay, Musabak, Engin, Gok & Kutlu, 2008).

In another study, seeking instrumental support has been linked with lower scores in depression (Arran, Craufurd & Simpson, 2013). Inspection of the factor loadings confirm that the items that possess higher loadings relate to symptoms of anxiety and psychological HRQoL when comparing with items that relate to depression, coping and emotional representation of illness. It may be the case that anxiety is a significant facet of psychological health in this population. This may be supported by analyses in the present study that may point to the presence of anxiety state in this population.

Factor 3: Illness management behaviours

This factor integrates seven items that reflect a combination of illness management behaviours indicating good internal reliability (.86). The importance of coping and its strategies (e.g. active coping, planning, emotional support, instrumental support, venting and humour, have been cited throughout the thesis, and widely cited in the chronic illness literature (Kaltsouda et al., 2011; Büssing, Ostermann, Neugebauer & Peter Heusser, 2010; Endler, Kocovski & Macrodimitris, 2001; Rutter and Rutter, 2002; Carver, 1997). The present study indicates that PA sufferers may have engaged more in adaptive coping when compared to maladaptive coping.

Factor 4: Illness controllability and support

This factor consists of three items reflecting illness controllability and support. It includes two items from the Brief-IPQ, personal control and treatment control, as well as one item that represents satisfaction with personal relationships in the WHOQOL-BREF. Previous literature has suggested the importance of illness beliefs about controllability in the management of disease (Weldam, Lammers, Heijmans & Schuurmans, 2014; Taylor, 2009). Studies have suggested patients feeling that their illness was controllable, both personally and through treatment (Morgan, Villiers-Tuthill, Barker & McGee, 2008). Other research has found that perceptions of personal control over one's illness have been found to be lower than perceptions of treatment control (Hopman & Rijiken, 2015). In other studies, weaker beliefs about one's illness control was associated with lower HRQoL (Rutter & Rutter, 2002). Higher perceived control regarding one's condition has also been linked with support in assisting with the same (Joseph, Neeraj & William, 2014).

Individuals' perceptions of absence of support have also been linked to higher perceived need of treatment. Pilot studies in the present thesis have suggested that PA sufferers being dissatisfied with PA management and seeking online support to help them deal with the life disruptions posed by PA.

Even though the internal reliability for this factor may be relatively low (.46), it highlights the importance of patients' perceived control, how treatment may help control the severity of symptoms, and support through personal relationships. Examination of the factor loadings indicated that personal relationships had the lowest loading onto the overall factor. The examination of correlation coefficients indicated low non-significant associations of personal control with both perceived control and treatment control. Previous studies looking at support provided by a significant other suggested that in some cases, the type of support provided may inhibit the sense of control and adjustment of the patient. This may be explained through the display of overprotective behaviours which may increase psychological distress in the person receiving the support (Meier, Bodenmann, Mörgeli, & Jenewein, 2011; Schokker, Links, Luttik & Hagedoorn, 2010). Perceived control and treatment control shared similar loadings and significant moderate correlations. Higher perceived control has also been associated with better self-management of illness (Kaptein, Klok, Moss-Morris & Brand, 2010). This may be the case for PA patients who may not get treatment according to their needs and resort to self-treatment. The cognitions included in this factor reflect crucial themes that emerged from qualitative pilot work and existing research (Hooper, Hudson, Porter & McCaddon, 2014).

Factor 5: Maladaptive coping

Factor 5 comprises 3 items from the Brief-Cope (substance use, denial and venting) and the internal reliability for this factor was moderate (.66). These coping styles are well documented in the literature, reflecting the challenges of dealing with a diagnosis of chronic illness (Cameron & Wally, 2014). Tuncay, Musabak, Gok & Kutlu (2008) have reported the use of denial and substance use in patients suffering with diabetes. This study also reported the use of venting, however this was perceived as an effective way to promote psychosocial wellbeing in this patient group. Alternatively, in patients experiencing chronic fatigue syndrome venting was associated with greater disability and poorer psychological well-being (Moss-Morris, Petrie & Weinman, 1996). The detrimental use of venting has also been reported in other population groups (Kaltsouda et al., 2011; Büssing, Ostermann, Neugebauer & Heusser, 2010). Freeman et al., (2016) have associated patient denial with worse visual field, when assessing the progression of glaucoma. The experience of heart failure was associated with denial in a narrative review of qualitative studies (Jeon, Kraus, Jowse & Glasgow, 2010). Qualitative research reported patient engagement in substance use as a way of dealing with different chronic conditions. The use of alcohol and prescription medications to deal with the associated stress has been reported by Jacobs, Ownby, Acevedo and Waldrop-Valverde, 2017).

Research has also suggested that patients with rheumatoid arthritis self-managed their illness by buying over-the-counter medication to relieve their perceived symptoms (Townsend, Backman, Adam & Li, 2016).

Other studies with other patient groups reported increased substance use at the time of diagnosis and denial as barriers to treatment entry (Kuchinad et al., 2016). In the present study approximately 80% of the population reported 'substance use' 72% reported using 'denial' and the use of 'venting' was recorded for 42%, all to a lower extent. This may be linked to self-management in PA patients that are unable to get additional treatment, however only a small percentage (13%) of PA sufferers reported self-managing their condition.

Factor 6: Illness understanding and adjustment

Illness understanding and adjustment represents factor 6, comprising of five items. These items include acceptance coping, illness coherence and environmental HRQoL (availability of information and healthy physical environment). Literature has previously emphasized illness understanding as an important cognition through the course of one's illness, facilitating one's adjustment (Kostova, Caiata-Zufferey & Schulz, 2014; Pierobon, Giardini, Callegari & Majani, 2011; Morgan, Villiers-Tuthill, Barker & McGee, 2008; Sharpe & Curran, 2006). Illness responses such as acceptance are common in patients suffering with long-term conditions and may be explained by positive experiences of diagnosis, treatment and appropriate social support (Spessotto et al., 2016; Barton et al., 2009; Cheek & Oster, 2002).

Factor 7: Distraction

This factor is composed of four items that reflect spirituality and self-distraction. Spirituality has been suggested as a resourceful way of dealing with a chronic condition, being a key component of holistic care. Seeking meaning through spirituality has been suggested as a resourceful way of coping with chronic illness, being associated with improved health-related quality of life (Büssing & Koenig, 2010; Cohen et al, 2007). A qualitative study based on descriptive phenomenology have suggested that engaging in faith, prayer and seeking related sources of support, reflected patients' lived experience with their chronic illness (Narayanasamy, 2013; Büssing & Koenig, 2010;Cohen et al, 2000). Self-distraction has been reported to be one of the most used strategies by diabetic patients (Tuncay, Musabak, Gok & Kutlu, 2008). Self-distraction and spirituality have been used as a meaningful way of diverting attention from illness demands (Gemmell et al., 2016).

The Pernicious Anaemia health-related quality of life questionnaire (PA-HRQoL)

The following statements relate to the extent to which your life has been affected by your Pernicious Anaemia (PA), your experience of symptoms and how you may have dealt with it, in the past four weeks. Please select the most appropriate answer that fits your personal situation. There are no wrong answers. If a statement does not apply to you please select 'No, not at all'.

	Extremely	Very much	Moderately	A little	No, not at all
1. My illness has affected my life					
2. I have had comfort and understanding from someone					
3. I have found comfort in my religion or spiritual beliefs					
4. I have felt as if I am slowed down					
5. I have experienced a frightened feeling as if something awful was about to happen					
6. I have felt tense or 'wound up'					
7. I have made fun of the situation					
8. I have had constipation, loose bowels or diarrhoea					
9. I have felt that treatment controlled my illness					
10. My physical environment has been healthy					
11. I have felt tired or had little energy					
12. I have given up trying to deal with my illness					
13. I have thought hard about what steps to take					
14. Worrying thoughts went through my mind					
15. I have learnt to live with it					
16. I have looked forward with enjoyment to things					
17. I have used alcohol or other drugs to help me get through it					
18. I have had emotional support from others					
19. I have felt breathless					

	Extremely	Very much	Moderately	A little	No, not at all
20. I have prayed or meditated					
21. I had trouble falling or staying asleep or sleeping too much					
22. I have been able to laugh and see the funny side of things					
23. I have felt pins and needles					
24. I have felt that the information I need is available in my day-to day- life					
25. I have felt numbness (extremities)					
26. I have turned to work or other activities to take my mind off things					
27. I have experienced sudden feelings of panic					
28. I have felt I am able to control my illness					
29. I have refused to believe that it has happened					
30. I have been satisfied with my personal relationships					
31. I have had negative feelings such as blue mood, despair, anxiety, depression					
32. I have felt chest pain					
33. I have felt that I have a good understanding of my illness					
34. I have experienced a sort of frightened feeling like 'butterflies' in the stomach					
35. I have had help or advice from other people					
36. I have said things to let my negative feelings escape					
37. I have accepted the reality of the fact that it has happened					
38. I have expressed my negative feelings					
39. I have been able to enjoy a good book or radio or TV programme					
40. I have done something to think about it less, such as going to movies, watching TV, reading ,daydreaming, sleeping, or shopping					
41. I have concentrated my efforts on doing something about my illness					
42. I have had memory problems, such as difficulty in concentrating					
43. I have tried to get advice or help from other people about what to do					

Table.6.6.1.3 The preliminary version of the PA-HRQoL questionnaire© with 43 items

Table 6.6.1.4

Scoring instructions for the PA-HRQOL questionnaire

Domain	Items	Range
Domain 1 Physical functioning	1,4,8,11,16,19,21,23,25,32,42	0-44
Domain 2 Illness impact on psychological health	5,6,12,14,22,27,31,34,35,39	0-44
Domain 3 Illness management behaviours	2,7,13,18,38,41,43	0-28
Domain 4 Illness controllability and support	9,28,30	0-12
Domain 5 Maladaptive coping	17,29,36	0-16
Domain 6 Illness understanding and adjustment	10,15,24,33,37	0-16
Domain 7 Distraction	3,20,26,40	0-16

6.7 General discussion

The present study aimed to investigate the impact of illness severity on patients' health-related quality of life. These investigations helped to identify the best predictors of HRQoL in the PA population and specifically served as basis for the development of a patient-centred instrument for the identification and management of health-related quality of life for patients suffering with pernicious anaemia, the PA-HRQoL questionnaire. PA poses a considerable impact on individuals' lives and these impacts have not previously been assessed. The present study has described the development of a new patient-centred instrument to identify and assess the health-related quality of life of patients suffering with PA (PA-HRQoL). The PA-HRQoL is a novel measure based on patient-reported outcomes and it has the advantage of potentially identifying issues that may not be assessed in generic HRQoL instruments or during the clinical consultation (Heijmans et al., 2001). Its content resulted from the initial generation of factors from existing validated measures, and pilot work, ensuring that items included were pertinent to the PA population. This measure consists of 43 items measured across seven domains (physical functioning, illness impact on psychological health, adaptive management behaviours, illness controllability and support, maladaptive coping, illness understanding and adjustment and distraction) and it appears to be reasonably short and practical to use in clinical settings.

Findings from the present study demonstrate the important relationship between health status, illness representations and coping as important determinants of HRQoL. In the PA population, HRQOL seems to be determined by patients' beliefs about their condition, which in turn motivate behaviours consistent with disease management and as a result, may elicit anxiety and depression responses.

Nevertheless, these findings lend support to the common sense model described by Leventhal and colleagues (1980). However, it also becomes difficult to identify the cause of poor or improved functioning. Using these constructs as central determinants of outcome is warranted in future longitudinal research (Petrie & Weinman, 2012).

Measures of health status (anxiety and depression) emerged as significant negative predictors of physical, psychological and environmental health. Investigation of the levels of anxiety and depression in this sample indicated the possible presence of a depressive and anxious state in this population. One may argue that this may not seem surprising since negative affect is common among all disease groups, compared with the general population (Yuan, Yu, Shi, Ke & Zhang, 2015; Katon, 2011; Clarke & Currie, 2009). Nonetheless, this emphasizes the need of identifying patients that may experience troubles dealing with the impact of PA, so that appropriate psychosocial support can be provided (Snaith, 2003).

The current study has also presented statistically negative associations between illness consequences and physical, psychological and environmental HRQoL. The experience of symptoms and psychosocial difficulties as part of the chronic aspect of one's condition may have resulted in psychological distress and therefore impaired HRQoL (Nabosi, Wardam & Al-Halabi, 2013). Alternatively, significant positive associations were found between illness identity and the psychological and environmental dimensions of health-related quality of life. In this way, PA sufferers' illness understanding may be a contributing factor to an improved HRQoL. Environmental HRQoL includes items that cover health care and informational support. Pilot work and existing PA research, however limited (Hooper, Hudson, Porter & McCaddon, 2014), has previously emphasized the lack of satisfaction with the current provision of support. These findings have also been documented elsewhere in other population groups (Kaltsouda et al., 2011; Cartwright, Endean & Porter, 2009; Dickson, Knussen & Flowers, 2007). Intervention studies aiming to help patients develop effective coping strategies would be valuable for this population. Previous research has reported the beneficial effects of a psycho-educational intervention programme addressing health-related quality of life in patients experiencing symptom burden. Improved health status, better illness understanding and feeling less isolated were reported as the main benefits of this intervention (Lindell et al., 2010). The results discussed here highlight the importance of measuring health-related quality of life in populations suffering from chronic conditions such as the one under investigation (Rawlings, Brown & Reuber, 2017).

One significant finding related to the potential impact of illness controllability and support on HRQOL. This finding may imply that improvements in one's perceived personal control may improve PA management, resulting in improved relationships and better HRQoL. Research may also focus on assessing the provision of health care support in this population. Assessing patients' needs in relation to their expectancies of support has been suggested as an important part of disease management (Bonevski et al., 2000; Girgis, Boyes, Sanson-Fisher & Burrows, 2000). Findings from a needs assessment with patients suffering from renal complications has found emotional, physical, psychological, social and existential burdens. These findings served as basis for the future development of a health psychology service in concurrence with a renal counselling support within hospital services as ways of improving services to renal patients (Finnegan-John & Thomas, 2012). Future research may also implement prospective studies to investigate whether illness representations mediate symptom severity.

Coping styles have emerged significantly in the factor structure, being included in different factors. It is important to note that there appears to be an overlap regarding the coping styles that emerged in factor 3 (illness management behaviours) and factor 5 (maladaptive coping). An example, the two items that represent venting, one loaded in factor 3 ('I've been expressing my negative feelings') and one loaded in factor 5 ('I've been saying things to let my unpleasant feelings escape'). Even though these items represent the same coping style, it may be the case that these items may have been perceived differently by the participants.

The design employed in the present study may be a possible explanation. Factor analysis of different set of items, may have reduced coping styles into apparently different concepts. This is shown on factor 3, 5 and 7 (e.g. religion and self-distraction). Previous psychometric assessments of the COPE questionnaire (Carver et al., 1989) have documented this issue (Lyne & Roger, 2000; Ingledew et al., 1996).

Co-morbidity presence remains an issue in this population. More than half of the sample (55%) reported being diagnosed with another chronic condition. This may impact on the present findings, as it is not clear whether patients differentiated PA symptoms from existing co-morbidities. Previous research has suggested co-morbidity presence to result in poor psychological health and increased symptom severity, resulting in impaired HRQOL (Huber, Wacker, Vogelmeier & Leidl, 2015; Blinderman et al, 2009). It would be useful to investigate PA patients with no other existing conditions. However, this may prove difficult regarding the likelihood of co-morbidity in chronic conditions (Katon, 2011) and in PA (Hooper, Hudson, Porter & McCaddon, 2014; Alkhateeb et al, 2003; Zelisseen et al, 1995). Therefore, firm conclusions may not be drawn regarding the HRQoL of these patients.

Limitations of the measures included in the present study refer to the fact that illness perceptions' dimensions' were only measured by using one item. This may lack clarity in terms of the underlying explanations for specific dimensions such as 'illness consequences'.

Employing the previous version of the same measure (IPQ-R; Moss-Morris, Weinman, Petrie, Horne, Cameron & Buick, 2002) where dimensions consist of more items, would have possibly been more precise (Fuchs & Diamantopoulos, 2009). Qualitative investigations into illness consequences would also prove useful in terms of potentially overcoming this limitation. This will be addressed in further studies, specifically when piloting the PA-HRQoL questionnaire.

The multidimensional locus of control scales only produced significant marginal correlations with the other variables in the present study. Even though the scale possessed acceptable internal reliability in this population group, it failed to capture perceptions of control in the analyses conducted. However, these were captured by the control dimensions in the Brief-IPQ. This may be explained by the population group and design used. Nonetheless, these scales are used to supplement other locus of control measures. It has been suggested that for specific population groups, investigation of only one dimension would possibly yield better results.

Further, this scale may produce better findings when applied to the investigation of specific health behaviours (Wallston, Wallston & Devellis, 1978).

Limitations of the present study refer to the cross-sectional nature of the study design in which arguments about causality may not be drawn. Further, since no objective data regarding illness severity was gathered, further discussion of the impact of psychological factors is not possible. Although the current study used an adequate powered sample for conducting the required analyses, the sample size was potentially limited to conduct comparisons between sub-groups of patients in different stages of their condition.

Exploring these psychological variables longitudinally may have produced different results, if the effect of treatment was considered in these patients. Research with patients suffering from comorbid depression and diabetes receiving treatment for depression, were part of an intervention aimed at improving diabetic outcomes. The intervention was based on providing education, problem-solving treatment and support for managing antidepressant medication. Functional impairment and diabetes self-care behaviours were assessed at baseline, 3, 6 and 12 months. Patients presented with less severe depression and improved on their overall functioning (daily activities' performance) at 1-year post-intervention, as compared with individuals receiving usual care (Williams et al.,2004).

Due to a low response rate in the clinical population, the findings of the present study are limited to infer generalizability. Nevertheless, part of the sample included non-NHS patients. This has both advantages and disadvantages. The online sample recruited from patient support groups, was a diverse one and it may have been representative of the PA population.

However, it may also bias the results of the study, meaning that individuals that are affiliated to support networks may express more illness concern. Advantages of using an online social networking population means that the experience of both clinic and non-clinic individuals is reflected in the developed instrument.

HRQoL has been suggested as an important health indicator in clinical outcomes. Some of the studies presented in this section used disease-specific measures of HRQoL, which in a way may have provided better support for their findings. However, it has also been suggested that the combined application of both generic and disease-specific measurements may result in more accurate investigations of both global aspects and specific dimensions of HRQOL, covering all areas of functioning (Engstrom, Persson, Larsson & Sullivan, 2001; Milligan et al., 1993). Taking this into account, since there is no current validated measure of HRQoL for the PA population, the only way of assessing HRQoL at this point in time was to use a well-established generic measure like the WHOQOL-BREF.

6.8 Conclusion

The current study emphasizes the interrelationship between the dimensions of HRQoL and mainly indicates the contribution of illness identity, treatment control, illness consequences and depression to explaining psychological HRQoL, and the influence of illness consequences and anxiety in explaining environmental HRQoL. Research findings recognize the importance of considering the impact of a chronic condition such as pernicious anaemia on psychological health and reinforce the knowledge that improved psychological health may predict improvements in HRQoL (Blakemore et al, 2014). The present study contributes to a growing body of literature emphasising the importance of investigating patients' beliefs regarding their overall illness experience, when developing patient-centred treatment pathways. The preliminary version of the PA-HRQoL questionnaire was developed for the PA population. However, this only represents the early stages of instrument development. Further research will focus on the validation of this instrument in a sub-sample of PA sufferers to establish appropriate psychometric properties. Subsequent instrument refinement will allow items to be added or removed in subsequent versions. The outcome of the research presented in this thesis may represent significant advances in the PA care by supplementing existing approaches to the PA management.

Chapter 7

General discussion

7.1 Summary of findings

The work presented in the current thesis was carried out to address the limitations in the existing research concerning the psychosocial impact of pernicious anaemia on individuals' health-related quality of life. The primary endpoint reflected the development of a patient-centred outcome measure to identify and manage HRQoL in patients suffering with this condition, the PA-HRQoL questionnaire. This objective was achieved through conducting four exploratory studies to further understand why patients still experience severe symptoms and perceive the need for additional B₁₂ therapy, despite frequent treatment. The findings of these studies align with empirical evidence and highlight the contribution of illness representations, coping styles and health status to the understanding of health-related quality of life in this population.

Study 1 (investigating the demographic profile of patients suffering with B₁₂ deficiency) investigated the progression of patients from diagnosis through treatment and clinical management of this condition. There were gaps identified in the patient records mainly relating to specific diagnostic testing, which may not have been carried out consistently for this population. Further, information regarding clinical variables such as family history and the reason why treatment was discontinued for some patients despite a PA diagnosis is lacking for the majority of cases.

This study highlighted the diagnosis of comorbidities, in particular, depression, contributing to the experience of psychological distress in this patient group.

These findings indicate that PA screening may not be routinely performed, having significant implications for the effective management of PA.

Study 2 (investigating individuals' perceptions of their PA experience) was carried out to explore specific questions of diagnosis and treatment that emerged from the findings of study 1. The themes that surfaced from this study included transitions to PA diagnosis, PA beliefs, B₁₂ therapy and symptom experience and management. This study suggested poor practices in the management of PA, resulting in misdiagnosis in many cases. This contributed to exacerbated symptoms, illness progression, and social isolation resulting from the lack of perceived clinical support. The severity of symptoms and the inability to control these represented key factors in the way individuals coped with PA. Pernicious anaemia imposed restrictions on activities of daily living, impacted on the ability to establish social relationships, contributing to the experience of psychological distress and resulting in less confidence in the ability to deal with this condition. Nevertheless, for some individuals, lifestyle changes such as exercising and changing one's diet, helped to cope with the severity of symptoms. Findings from this qualitative study highlighted locus of control, coping, quality of life and social support as meaningful variables to be further explored.

Subsequently, study 3 (A study of the PA experiences of members of the Pernicious Anaemia Society) delved into the diagnostic and treatment perceptions of members of the PA society. The themes that emerged from this study included misdiagnosis, PA diagnosis, B₁₂ therapy, symptom management, provision of information and support from local health services and relationships. Findings suggested that patients' subjective experiences were trivialized and that reported symptoms were attributed to psychosomatic causes, by GP's. This resulted in increased patient anxiety, influencing coping responses such as ignoring symptoms, suffering in isolation and buying OTC treatment to alleviate perceived symptoms.

Although individuals expressed the relief and regained sense of self from finally receiving a PA diagnosis, lack of confidence in the medical profession, in terms of effectively identifying and treating pernicious anaemia was also expressed. Treatment suspension reflected an important sub-theme, compromising individual care. Some patients reported treatment being interrupted by their GP, despite PA diagnosis, resulting in poor clinician-patient encounters and influencing decisions for the self-management of their condition. Some patients also expressed worry concerning the prognosis of their condition. An area of future research may be to explore the significance of prognosis over time and its potential association with the development of gastric cancer, a significant concern in this population. Treatment dissatisfaction and the lack of healthcare support represented common complaints of many PAS members'. Results of this study highlighted the perceived suboptimal management of PA.

The outcomes of study 1, 2 and 3 provided the foundations for selecting the psychosocial constructs measured in study 4 (investigating illness severity and health-related quality of life in patients diagnosed with Pernicious Anaemia), which included illness perceptions, health status, coping strategies, locus of control, somatic focus and health-related quality of life. Investigations into these variables suggested health status, illness representations and coping as key determinants of HRQoL in this population. Findings indicated that depression and anxiety responses were elicited by patient's beliefs about their condition resulting in specific illness responses.

Key findings from these investigations indicated that treatment control and depression significantly explained psychological HRQoL and anxiety and illness consequences explained environmental HRQoL. These findings support the idea that improvements in the management of PA may predict improvements in psychological health and subsequently improvements in HRQoL. The variables in this study were ultimately subjected to data reduction techniques and provided meaningful factors that formed the basis of the PA-HRQoL questionnaire. This prototype is comprised of 43 items across seven dimensions (physical functioning, psychological health, illness management behaviours, illness controllability and support, illness understanding and adjustment, maladaptive behaviours and distraction), measured on a 5-point Likert scale. Physical functioning was associated with perceived illness consequences, symptom severity and depression. The dimension of 'illness impact on psychological health' explains the association between behaviour disengagement and its association with the perceived experience of anxiety and depression.

This relationship appears to be mediated by instrumental support. Illness management behaviours reflect the importance of different types of coping strategies used to deal with PA. These include active coping, planning, emotional support, instrumental support, venting and humour. The dimension of 'illness controllability and support' reflects the link between personal control, treatment control and the provision of support. Patients' beliefs of being supported and that their illness may be controllable, both personally and through B₁₂ therapy, contribute to improved HRQoL. Maladaptive coping reflects the challenges faced by PA sufferers in dealing with their condition, such as engaging in denial and substance use. Illness understanding and adjustment are associated with illness acceptance, resulting in improved HRQoL.

Lastly, distraction highlights the use of coping styles that may help the individual cope with illness demands, such as self-distraction and seeking meaning through spirituality. These dimensions substantiate the themes that emerged from the studies already described here, strengthening the content validity of this instrument, and highlight the importance of psychological constructs in the development of patient-centred pathways. Each dimension taps into specific areas of HRQoL that are meaningful to PA sufferers, may be assessed individually, or evaluated in a therapeutic context on an item by item basis (Lambert and Shimokawa, 2011; Harmon et al., 2007). The PA-HRQoL was developed to complement existing physiological approaches through highlighting poor functioning on a wider level potentially informing the development of psychosocial interventions.

7.2 Potential limitations

The literature suggesting a higher prevalence of PA diagnosis in females is mixed (Lahner & Annibale, 2009; Zittoun, 2001; Carmel, 1996). The fact that the sample used was predominantly female, may have influenced the outcome of the research. This may be partly explained by gender differences in seeking health behaviour (Thompson et al., 2016; Schetzer & Florcken, 2012; Regitz-Zagrosek, 2012; Zandman-Goddard et al., 2012). Research suggests that in comparison with men, women seek health care more frequently for both physical and mental health complaints (Mackenzie, Gekoski & Knox, 2006, Verhaak et al., 2005). Gender may indirectly influence health care utilization through factors such as a higher propensity to seek health care services, the experience of somatic morbidity and poor perceived health status (Nabalamba & Millar, 2007; Koopmans & Lamers, 2006; Carriere, 2005).

A strength of the current research refers to the recruitment of both clinic and non-clinic samples with a varied age range and a broad range of educational attainment, which may have helped strengthen the findings. However, accounts of individuals that do not have access to the internet (BPS, 2013; Wright, 2005), and the potential tendency of individuals overstating or understating responses may have resulted in self-selection bias (Fricker, 2008).

7.3 Implications of research findings

The results of the studies that form the current thesis provide a better understanding of this condition and contribute to the development of a novel instrument based on patient-reported outcomes. This has further implications for the management of PA. Currently, the provision of healthcare support may be poor for PA patients in general and most specifically for the ones that perceive the need for additional treatment. These patients report experiencing dismissive attitudes from their clinicians, resulting in increased psychological distress, influencing decisions to withdraw their current care and opt for the self-management of their condition. By identifying patients that may be experiencing difficulties in managing their symptoms, the PA-HRQoL has the potential of adjusting treatment according to individual needs.

7.4 Directions for further research

In further research, the PA-HRQoL questionnaire will be tested in a subsample of PA sufferers to establish validity and reliability. According to Patrick et al (2011), assessing patient understanding represents a key feature on the development of patient-centred instruments. This iterative process includes ensuring that the content is clear and meaningful to the population under study and that respondents understand how to complete the instrument. This will allow for subsequent instrument refinement, establishing the content validity of the final version of the instrument, and extensive psychometric testing will be undertaken, which will include reliability analyses and sensitivity testing. Predictive validity refers to the extent to which results of a measure predict future outcomes (Jenkinson & McGee, 1998).

Since there is no gold standard measure for HRQoL in patients suffering with PA, other validation strategies will be considered, such as construct validity (Guyatt et al., 1993). Subsequently, further studies including a large number of patients will need to be carried out to ensure external validity. Once validated, the PA-HRQoL may be useful to identify and target individual patients that may be experiencing symptom burden and therefore be used as an outcome measure in clinical trials and in the assessment of illness progression. This instrument may be used to monitor individual patients and highlight patients in need of direct referral to other services to facilitate prompt and effective treatment.

Illness perceptions are not static, these may change according to individual circumstances. The research presented here may provide the starting point for developing interventions that integrate psychosocial support in the routine care of PA. This may be achieved by providing education and support in the management of PA.

Strengthening PA beliefs may result in better illness understanding. This may result in the improvement of symptoms and therefore improved health status, benefiting both the patient and physician in achieving optimal management and therefore improved HRQoL. Hence, interventions focusing on increasing patients' agency and health-related quality of life that can be rolled out across UK GP surgeries may prove valuable.

7.4.1. Validity and reliability testing of the PA-HRQoL instrument

The development of health-related quality of life measures considers the examination of the psychometric properties of i) reliability and ii) validity. Therefore, instruments must be reliable, valid and sensitive to change.

7.4.1.1 Reliability

Reliability is a prerequisite for validity and refers to the ability of a specific measure to produce consistent results under the same conditions. Reliability may be demonstrated by assessing the internal reliability (Cronbach's alpha) and by assessing test-retest reliability. The internal reliability assesses item homogeneity and it is determined by the Cronbach's alpha. Test-retest reliability is an important indicator of the stability of an instrument. It consists in the administration of the instrument to the same population, in two separate occasions. Since it is likely that symptom reporting fluctuates over time, intervals of four weeks are generally used to ensure that a change in true score is minimal. The correlation between the scores in two occasions will provide an estimate of the reliability of an instrument.

7.4.1.2 Validity

The validity of an instrument refers to its ability of measuring what is designed to measure. Fundamentally, there are four aspects to validity, face validity, content validity, criterion validity and construct validity (Field, 2009).

Face validity refers to the subjective assessment of the relevance of a specific instrument. It refers to whether items in a questionnaire appear to make sense and can be easily understood. Face validity of the PA-HRQoL was initially established in previous stages of this research, informed by the experience of PA sufferers, leading to the development of the PA-HRQoL.

Content validity examines the degree to which individual items represent the construct being measured and capture the concepts that reflect the experience of individuals (Patrick et al., 2011).

Criterion validity tests for the ability of an instrument to correspond with other valid measures (concurrent validity) as well as it tests for the ability to predict future outcomes (predictive ability).

Construct validity refers to the ability of an instrument to confirm expected hypotheses. It reflects the patterns of the relationships of a specific instrument with well-established measures. Construct validity may be divided into two sub-types, convergent validity and discriminant validity. Convergent validity reflects the agreement among ratings of measures, reflecting that they are theoretically related. Discriminant validity reflects the lack of a relationship between concepts that are not theoretically related, ensuring that measures can discriminate between different population groups (Ware et al., 1993; Brazier et al., 1992).

Responsiveness

Sensitivity to change constitutes an important criterion of HRQoL measures aiming to evaluate the impact of interventions. The depiction of change may vary according to different measures. This may be related to the content of a specific measure as well as its primary objective, such as evaluation of treatment (Fitzpatrick et al., 1992).

Validity and reliability testing of the PA-HRQoL instrument (ctd')

The psychometric properties of reliability and validity of the PA-HRQoL instrument will be tested in three different stages. In stage 1, content validity will be assessed through language clarity and respondent understanding. The measure will be administered to a sub-sample of PA sufferers recruited from the Pernicious Anaemia Society. Since there is no gold standard measure of HRQoL for patients suffering with PA, stage 2 will determine criterion validity of the instrument by testing the same with another well-established generic measure of HRQoL, in a cross-sectional study. The Short-form Health Survey (SF-36; Brazier et al., 1992; Ware & Sherbourne, 1992) has been widely and extensively used across different population groups due to its high psychometric properties of validity and reliability and therefore appears to be one of the best available instruments for the assessment of criterion validity of the PA-HRQoL instrument. In this stage, relationships between the scales will be examined through correlations (Pearson). Item correlations with scale totals will be investigated and the internal reliability of the scales will be determined (Cronbach's alpha). In stage 3, further validation will be carried out to establish reliability, construct validity and responsiveness. It is anticipated that responsiveness will be tested in a longitudinal study, by assessing change in health state scores from baseline to follow-up.

Stage 1: Piloting and modification of the PA-HRQoL to inform subsequent developments of the instrument.

Method

Design

Initial validation of the PA-HRQoL instrument will employ a cross-sectional survey design to test the psychometric properties of the PA-HRQoL instrument.

This instrument will be administered online to PA sufferers. This will ensure that respondents will have enough time to complete the measure and provide appropriate feedback allowing the refinement of the instrument in subsequent stages of its development.

Ethical considerations

Ethics for the stage 1 (pilot testing of the PA-HRQoL) have already been granted by the University of South Wales Faculty Ethics Research Sub-Group. Participants will be informed about the study purpose and will be able to withdraw from the study at any time (Appendix 4.2). Informed consent will be obtained via Survey Monkey, according to BPS guidelines (2010). Responses of potential participants will remain anonymous, as Survey Monkey does not retain IP data.

Sample

The sample will consist of PA sufferers recruited online from the PA society website. For inclusion, participants will be required to be at least 18 years of age, to have received a formal diagnosis of PA from a health professional, to confirm that they have not participated in phase 1 of the research study and to have an adequate understanding of the English Language. Exclusion criteria will include any inclusion criteria not met.

Sample size calculation

According to Baker (1994), a sample size of 10-20% of the original sample recruited for the study which led to the development of the PA-HRQoL measure (Study 4; N=184), constitutes a reasonable number of participants to consider enrolling in a pilot study. Since the primary objective of this study will be to pilot test the instrument, a sample calculation was based on the expectation that 37 reflects the minimum number of participants required for this pilot study.

Materials

The PA-HRQoL has been developed in Phase 1 of this research (study 4).

Procedure

Participants will be required to complete the measure online and provide written feedback on the content and format of the measure to ensure acceptability and practicality.

Data analysis

Descriptive statistics will be computed to identify frequency distributions and dispersion of scores. The reliability of the instrument (PA-HRQoL) will be determined by using the Cronbach's alpha statistic and validity. Item-total correlations will be determined to establish content validity.

7.5 Contributions to the PA literature

Despite potential clinical advances that may inform a more effective approach to the management of PA, such as the issue of new guidelines (Devalia, Hamilton & Molloy, 2014) , and new ways of interpreting test results (Fedosov, Brito, Miller, Green & Allen, 2015) , the current management may not be effective in the control of PA. The current thesis represents advances in the PA literature and is the first to effectively address individuals' perceptions of their PA experience. PA research has been extended in terms of i) developing a better understanding regarding the pathway from diagnosis through treatment and management of PA, ii) highlighting the centrality of psychological variables in determining HRQoL, iii) creating a greater awareness of PA, calling for clinicians' willingness to adopt a holistic approach to the management of pernicious anaemia, therefore strengthening the doctor-patient relationship, iv) developing a patient-centred measure for the identification and management of HRQoL in PA patients. The PA-HRQoL is a novel measure based on patient-reported outcomes, emphasising meaningful aspects of ones' illness and has the potential of i) complementing existing approaches to the management of PA ii) assessing the severity of patients' symptoms, therefore providing tailored care subsequently improving patients' health status , iii) identifying issues that may not be assessed in generic HRQoL instruments or during the clinical consultation, iv) targeting individual patients' needs and improving coping strategies through the development of interventions, v) assessing HRQoL changes over time, and, vi) reducing the economic costs associated with the burden of disease at primary and secondary levels.

Chapter 8

General conclusion

The current thesis has demonstrated the crucial impact of PA in influencing beliefs regarding illness controllability and eliciting coping responses subsequently determining one's health status and HRQoL. Hence, illness management that addresses PA sufferers' needs from a biopsychosocial perspective may contribute to higher satisfaction with treatment, resulting in improved health-related quality of life. The current thesis has generated discussion on how current practices may be improved and described the development of the PA-HRQoL, a novel patient-derived health-related quality of life measure intended to assess and manage symptom severity in a complex condition such as pernicious anaemia. It includes domains that tap into interconnected areas of HRQoL including physical functioning, coping styles, illness controllability and support. Despite the potential limitations, the PA-HRQoL questionnaire is the first attempt to identify and manage HRQoL in this population group, reinforcing the growing body of literature in this topic area. The goal of the current thesis was achieved, and following appropriate stages of instrument refinement, the timely implementation of the PA-HRQoL is called for. It is anticipated that the PA-HRQoL may be used in routine clinical practice and provide health professionals with a further understanding of the health care needs of this population, serving as guidance for decision-making and the effective management of pernicious anaemia.

Glossary

Adenosylcobalamin	One of the active forms of B ₁₂ . As a supplement, only available in the form of tablets, not injections.
Anaemia	A reduction in the haemoglobin in the blood cells. The most common form of anaemia is iron-deficiency anaemia resulting in fatigue symptoms and small red blood cells. Fatigue is also common symptom in pernicious anaemia.
Antibody	Also known as, immunoglobulin is a large, Y-shaped protein produced mainly by plasma cells. This protein is used in the immune system to neutralize pathogens such as bacteria and viruses.
Atrophic gastritis	Chronic inflammation of the stomach mucosa, impairing the secretion of essential substances such as the intrinsic factor, resulting in digestive problems.
Cobalamin	The term used to describe vitamin B ₁₂ , due to the presence of mineral cobalt in the B ₁₂ molecule. Cobalamin exists in different chemical forms.
Cyanocobalamin	Represents a synthetic form of B ₁₂ , being produced from hydroxocobalamin and cyanide. This form is mostly produced in France and it is mainly added to fortified foods.
Hydroxocobalamin	The purest form of B ₁₂ , being produced by fermenting bacteria and it represents the main form of B ₁₂ found in most foods. It converts to methylcobalamin in the body and it is widely used as a standard treatment for pernicious anaemia.
Intrinsic factor	A glycoprotein secreted by the parietal cells. It is essential for the absorption of vitamin B ₁₂ . Failure to secrete the intrinsic factor leads to depletion of vitamin B ₁₂ and results in pernicious anaemia.
Methylcobalamin	Represents the most active form of B ₁₂ in the body and effective in protecting the nervous system
Parietal cell	Cells present in the stomach lining that produce intrinsic factor as well as hydrochloric acid. This acid is essential for breaking down proteins in the stomach, enabling the release of vitamin B ₁₂ from food.
Pernicious anaemia	Also known as autoimmune metaplastic atrophic gastritis, occurs when the individual produces antibodies that destroy the parietal cells in the stomach.
Subclinical	A suspected disease with no definite signs and symptoms.

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Appendices

Study 1

Appendix 1.1 – Authorisation for data usage

From: David Blower [mailto:David.Blower@gp-w95010.wales.nhs.uk]
Sent: 16 December 2011 14:05
To: Vinod Devalia (ABM ULHB - Pathology)
Subject: Data usage

Hi Dr

Dr Donagh has asked me to send this email as confirmation of our acceptance for you to go ahead and use the data you require.

Regards

Dave Blower

Business Manager

Oak Tree Surgery

www.oaktreesurgery.com

Appendix 1.2 – Example of routinely collected data

I D	AG E	GENDER/B ACKG	STAT US	POSTC ODE	B MI	BP(mm /hg)	Blo od typ e	FH	LIFESTYLE	
									SMO KE	DRINK(u/w)
1	84	Female, Welsh	Marri ed			120/60		Diabe tes Asth ma	No	Occasi onal
Problems: PA(29.10.07) Acne rosacea Anaemia Bronchitis Diverticular disease Myeloma					Testing: last on 2010					
Signs/symptoms: Abdominal pain Extreme tiredness Gait/balance Pins and needles vomiting					Values: 2008 B ₁₂ - 287					
Medication: B ₁₂ 1mg every 3 months, loading doses every 2 days/2 weeks, regular since diagnosis(rg)					Consultations since diagnosis 7(4 years) app 2/year					
Reason for B ₁₂ therapy: PA					Referrals: Orthopaedics					
Request for B ₁₂ : NS					Observations: Medication review on a regular basis. Reported feeling better with B ₁₂					

Appendix 1.3 – Example of classification of diseases and signs and symptoms (ICD-10)

Table 1. Disease classification

Classification	Examples
Blood and immune system	Iron deficiency anaemia
Circulatory system	Angina; Cardiac failure
Digestive system	Atrophic gastritis; Irritable bowel syndrome
Ear and mastoid process	Tinnitus
Endocrine, nutritional and metabolic	Folic acid deficiency
Eye and adnexa	Blurred vision; Cataracts
Genitourinary system	Chronic kidney disease;
Mental and behavioural disorders	Anxiety disorder; Dementia
Musculoskeletal system and connective tissue	Arthritis; Fibromyalgia
Nervous system	Cerebral atrophy; Epilepsy
Respiratory system	Asthma; Chronic obstructive pulmonary disorder
Skin and subcutaneous tissue	Alopecia; Eczema

Note: table devised according to the international classification of diseases (ICD-10).

Table 2. Signs and symptoms classification

Signs and symptoms	Examples
Circulatory and respiratory	pleurisy; shortness of breath
Cognition, perception, emotional state and behaviour	memory problems; hallucinations
Digestive system and abdomen	bowel problems; nausea
General signs and symptoms	abnormal weight loss; extreme tiredness
Nervous and musculoskeletal system	gait problems; tremors
Speech and voice	slurred speech; voice hoarseness
Skin and subcutaneous tissue	pins and needles; numbness
Urinary	dysuria; nocturia

Note: table devised according to the international classification of diseases (ICD-10).

Study 2

Appendix 2.1 – advert used to recruit PA sufferers

Hello,

I am undertaking research in the School of Psychology to explore the experiences of Pernicious Anaemia (PA) sufferers and to create a better understanding of the illness in order to improve treatment experiences. If you suffer from PA or if you know someone that would like to share their PA experience, and you can spare an hour of your time, please contact me to arrange an interview. Your views will be of great help to the research team and will be anonymous and strictly confidential, Thank you very much.

Kind Regards

Lenira Semedo (e-mail: lsemedo@glam.ac.uk)

Appendix 2.2 – Development of interview schedule

Interview Schedule: Exploring individuals' perceptions according to their PA experience

There is a lack of empirical evidence concerning the nature of psychological factors implicated in PA and questions regarding the understanding of the condition, its symptoms and variations in individual differences remain unanswered. Therefore, in order to create a better understanding of the illness and to be able to offer treatment regimes that meet the individual needs of each patient, the present interview sought to explore the experiences of these individuals regarding disease management. Psychological aspects in terms of coping with the illness, symptom perception and severity, locus of control, self-efficacy, illness beliefs and how these might guide symptom interpretation and the way patients adapt and cope with the condition, and quality of life will be the focus of this proposed interview.

1. Locus of control and chronic illness

Research has documented that individuals who exert control over their illness, experience the reduction of the side effects of their treatment (Carlson, 1977).

People with an internal locus of control (LOC) may be more likely to be more motivated, therefore engaging actively in efforts to gain control over their illness. However, it has been reported that this doesn't apply to chronically ill patients (e.g. cancer) who may experience frustration due to the inability to change their present health status. In contrast, individuals with an external LOC maintain a positive psychological state since they do not try to control the environment, therefore, frustration is less likely to occur (Wortman & Dunkel-Scheffer, 1979).

1. Quality of life and chronic illness

Coping with life changes and disease management often impairs quality of life (Sprangers et al, 2000). The impact of chronic illness threatens the quality of life of sufferers and consumes health care resources, therefore, information regarding the impact of chronic illness in the health related quality of life is crucial for obtaining patient-centred health services (Rice & Sung, 1996, as cited by Lam and Lauder, 2000). Quality of life is subjective, including domains of physical, psychological, daily role, social functioning and general health-perception (Department of Health and Human Services, 2000). One important aspect of quality of life refers to co-morbidity, where demographic factors such as time since diagnosis and age affect health perceptions (De-Bock et al, 1996, as cited by Lam & Lauder, 2000).

2. Illness beliefs and coping strategies

Illness beliefs and coping strategies are crucial factors in both the onset and progression of an existing condition as well as its outcomes. Patients beliefs about effective ways to manage their own illness may lead to a negative illness schema which may encourage processing of symptom- relevant information leading to misperception of the significance of these which may help to maintain negative illness beliefs (Moss-Morris, 2005).

Positive beliefs such as sense of internal control have been associated to coping strategies, which are generally considered more adaptive such as seeking social support and actively trying to tackle the problem. Converse strategies would be disengagement, avoidance and venting emotions. Research conducted with patients with CFS has reported that individuals normally exhibit emotion focused coping by adopting a defensive style.

However, it remains unknown if contribution to illness is due to a defensive style of coping or to suppression of emotion (Moss-Morris, 1996). Also, coping strategies were characterized as all-or-nothing erratic pattern of behaviour, being related to disability and fatigue (Moss-Morris, 2005).

3. Self-efficacy and chronic illness

Self-efficacy maintains that processes of psychological change operate through alteration of an individuals' sense of mastering efficacy (Bandura,1982).Patients who believe in their ability to master a situation look at challenges to control their illness, and these may be accomplished through mastering of situations, observing others and social persuasion .McCathie, Spence and Tate(2002) assessed coping strategies, levels of Self-efficacy regarding symptom management ,social support and adjustment(depression, anxiety and quality of life) in a sample of 92 individuals suffering from COPD . Controls used were: symptom severity, socioeconomic status, duration of disease and age and it was reported that high levels of withdrawal were associated to low levels of coping and self-efficacy and to high depression, anxiety and reduced quality of life.

General questions

1. Demographics (age, gender, background, status, family history of PA)
2. May you please confirm that you have been diagnosed with PA.? How many years since your diagnosis?
3. Do you have any other conditions? Please expand.
4. Do you believe that you have been misdiagnosed prior to your PA diagnosis? Please explain
5. Have you been tested? Which tests were performed? Please explain.
6. Regarding PA, how often do you visit your GP?
7. Are you undergoing any treatment? For how long? Frequency? Please expand. If not, have you ever been treated? If discontinued, why?

Questions regarding Illness perceptions (understanding of the condition, beliefs regarding testing/treatment, coping)

8. How knowledgeable would you say you are regarding your illness? Please expand (sources of information).
9. When diagnosed did you feel you were informed by your GP about your illness?
10. Did you look for a second opinion? Why/not?
11. What do you think is the cause of your illness? (i.e. genetic, stress)?
12. What do you think are the consequences of having PA? Do you think that it affects the way others see you or causes difficulties for those close to you?
13. Do you believe that your treatment regime is effective?
14. Did you ever have a break on the course of your treatment?
15. Have you ever asked requested for more (or less) treatment? How did your GP respond?
16. How does treatment affect your health? Please expand.
17. In relation to PA, do you think that it influences your lifestyle? What makes you feel better/worse?
18. How do you manage your symptoms? Please describe.
19. Are you aware of any support group for individuals with PA? Are you a member? If so, how helpful do you think it is?
20. Regarding family/friends support, do you feel that you are supported? Please expand.

Questions regarding symptoms (perception and severity)

21. What symptoms do you experience as consequence of having PA?
22. How would you describe the nature of your symptoms (frequency/severity/duration)?
23. Have you looked for information regarding your symptoms? If so, what have you found out? Did you find it helpful? Was it any different than you thought?
24. Would you say that your symptoms have changed (to better or worse) since time of diagnosis? How?

Questions regarding LOC and Self-Efficacy

25. In your opinion, what do you think has caused your illness? Please expand.
26. Do you think that you may have an effect on the control of your symptoms? Is there anything you do that makes you feel better?
27. Are you able to discuss your condition with your GP? If not, why (i.e. time constraint)?

Quality of Life and well-being

28. Do you think PA affects your quality of life?
29. Has PA changed the way you feel in any way? Please explain.
30. Have you experienced any limitations for doing your usual activities or tasks (inside or outside the home) because of your physical or emotional health? (Including social activities with family, etc.)?
31. Any other issues regarding your overall health?

Closure

32. To summarise, is there anything else that you would like to discuss that has not been touched upon?

Appendix 2.3 – Revised interview schedule

Introductory Note:

First, I would like to thank you for agreeing to participate in this interview. The purpose of this interview is to explore and understand the experiences of individuals with PA, as part of PhD research with the University of Glamorgan and ABMU NHS trust. All the information will be recorded remain confidential and will only be used by the research team for the purposes of dissemination. We would like you to answer the following questions as accurately as possible and to the best of your knowledge. The interview will last for about one hour. Should you wish to receive any feedback regarding the project; the research team will be able to respond to your request of information whenever possible.

My role is to help you to speak freely so you can share your views. I have some questions that will guide us through. Please note that these questions were designed for information only and do not intend to judge your answers in any way. If there are any questions that you do not wish to answer, I will respect that. I am not here to express my own views so please do not assume that my silence or nodding means I agree/disagree with you. Please let me know if you need a break or anything else that will help you feel more comfortable. Do you have any questions before we begin?

1. Demographics (age, gender, background, status, family history of PA)
2. May you please confirm that you have been diagnosed with PA? How long since your diagnosis?
3. Can you please explain the process leading up to the diagnosis? (Have you been tested? Which tests were performed?)
4. Do you believe that you have been misdiagnosed prior to your PA diagnosis? Please explain.
5. Can you please describe the process from one diagnosis to the other?
6. Are you undergoing any treatment? For how long? Frequency? Please expand. If not, have you ever been treated? If discontinued, why?
7. Regarding PA, how often do you visit your GP?
8. Do you have any other conditions? Please expand.
9. How knowledgeable would you say you are regarding your illness? Please expand (sources of information). Did you know anything about it prior to diagnosis?

10. When diagnosed did you feel you were informed by your GP about your illness? Was this beneficial?
11. Did you look for a second opinion? Why/not?
12. Do you feel you are able to discuss your condition with your GP? If not, why (i.e. time constraint)?
13. What do you think is the cause of your illness? (i.e. genetic, stress)?
14. What symptoms do you experience as consequence of having PA? Can you please describe the physical/emotional symptoms experienced?
15. How would you describe the nature of your symptoms (frequency/severity/duration)?
16. Have you looked for information regarding your symptoms? If so, what have you found out? Did you find it helpful? Was it any different than you thought?
17. Would you say that your symptoms have changed (to better or worse) since time of diagnosis? How?
18. How do you manage your symptoms? please expand
19. Do you think that you may have an effect on the control of your symptoms? Is there anything you do that makes you feel better?
20. Are you aware of any support group for individuals with PA? Are you a member? If so, how helpful do you think it is?
21. Regarding family/friends support, do you feel that you are supported? Please expand.
22. Do you believe that your treatment regime is effective? Please expand.
23. Did you ever have a break on the course of your treatment?
24. Have you ever asked requested for more (or less) treatment? How did your GP respond?
25. How does treatment affect your health? Please expand.
26. In relation to PA, do you think that it influences your lifestyle? What makes you feel better/worse?
27. Do you think PA affects your quality of life?
28. What do you think are the consequences of having PA? Do you think that it affects the way others see you or causes difficulties for those close to you
29. Has PA changed the way you feel in any way? Please explain.
30. Have you experienced any limitations for doing your usual activities or tasks (inside or outside the home) because of your physical or emotional health? (Including social activities with family, etc.)?
31. Any other issues regarding your overall health?
32. How has the PA experience been like for you?

Closure

33. To summarise, is there anything else that you would like to discuss that hasn't been touched upon

Thank you very much. Your views will be of great value to us.

Appendix 2.4 – Interview extracts

Interview 1

Y: And me I had it diagnosed for 7 years but it had started off with my hand swelling up, turning burgundy and clawing up. I would have been about 41-42 years old when that started maybe and nobody could sort it out, nobody understood what was happening and then they started to do B₁₂ injections with me and immediately it improved. It still aches but no longer swells up.

I: ok, so you were diagnosed 7 years ago and prior to that was there a different diagnosis?

Y: well, they have started treating me for a nervous breakdown, they have put me on antidepressants which were terrifying and I even didn't know my son when he came home from school one day and I didn't have the idea of where I was or what was happening and when I realised that they have told me what happened that I had this kind of blackout, which I didn't remember, I thought I will be troubled on my own and I didn't want any more tablets doing it, at least you know that is you.

I: ok, how long did it take from the diagnosis of nervous breakdown to the diagnosis of PA?

Y: oh, I would say it would be about 3 months and it was purely by chance because my sister had gone feeling very tired and they checked her B₁₂ and my sister had explained how I was and then they told her to tell me to get checked and that was it, and just under a 100 when they checked.

Interview 2

I: Ok then, so, shall we start then with... just tell me a little bit about the time when you were diagnosed and how long ago it was, just some of the things if you can remember around that time?

Y: Hum... I think it was about 13 or 14 years ago, I have been suffering from what I thought was a really bad depression and that even it is really difficult to remember because my memory was affected prior to my diagnosis. I think that I have been feeling really rough for about four or five years and I went to the GP and said I wasn't coping with life very well, I was tired, I was sleeping all the time, it was getting on the top of me. I wasn't coping with stressful situations very well, and with all fairness to the doctor, there was a lot going on with my life at the time, but at that time he diagnosed me with depression and he prescribed Prozac. I took that for about another year I suppose, because I think that I was just coming to the end of the Prozac, from what I can vaguely remember, I think that you have to take it for about that length of time. When I went back to him, I had an incident, I was driving the car, I was driving through town, I was driving at Newport road and I was going somewhere and I couldn't remember how to get there and I pulled over in the car and I started to cry, because I couldn't in my mind... you know how you sort of mentally map out a route...

I: yes, to somewhere that is familiar...

Y: Somewhere familiar and I was pulled in Newport road and I got really upset and I thought, obviously these Anti-Depressants aren't working. I went back to the doctors and at that point the doctor offered me a blood test. I got a call from the doctor about a week later saying please would I go in and see him, and he asked me if I was drinking.

I: drinking alcohol?

Y: drinking alcohol... and I think I would say 98% of the rest of the world. I do drink alcohol but I don't think that I never drank to excess... and said to me "do you drink?" and I said "yes" and then he said that he thought that I have been drinking too much and this might be something that I could consider getting out of control and then I might feel any better..

Interview 3

I: Ok, what do you think are the consequences of having PA? Do you think that it affects the way others see you or it causes difficulties for the ones around you?

Y: I don't really think that it impacts on my life that much, I suppose people are aware of it because... sometimes I find it very hard to concentrate before my injection so my productivity in work may drop and I think that the only person noticing it is my partner, because when I come home I just want to sleep, and I am laid on the settee and it might be a bit lonely for him because I am not that involved in the conversation, but I don't really think people consider it to be an illness like cancer or anything and they don't treat me differently

I: Do you believe that your treatment regime is effective?

Y: I have asked for more frequent injections in the past because there are some times when I feel I need more energy, I feel I need injections every two or two and a half months rather than the three -monthly

I: And what was the outcome of your request?


Y: I have asked for 3 times now and every time I got the same thing which is that they are not willing to give it to me more frequently because you can become dependent, according to the GP, the more frequently I get an injection, the more frequently I need one, they think it is psychological, I have been told that because my Folate levels and B₁₂ levels are so high that the symptoms I experience are psychological, so they are not willing to give me more injections.

I: Ok, after they have refused to give you more treatment you have stopped asking for more treatment? And did it have an impact on the way you felt?

Y: Hum... it's not very nice being told by a GP... for example normally my feet and toes go numb and they say it might be a psychosomatic side effect, not to worry about it, but it doesn't make you feel very nice... I know how GPs are like sometimes, they have certain opinions and I just take it with a pinch of salt and get on with it.

Study 3

Appendix 3.1 – Advert to recruit PAS' members



A research student from the University of South Wales, Lenira Semedo, is conducting research on the diagnostic and treatment experiences of Pernicious Anaemia. Lenira would appreciate your help. Please follow the link below in case you would like to take part.

Appendix 3.2 – PAS survey (posted online on survey monkey)

Welcome

Welcome and thank you for taking part in this research project. It aims to create a better understanding of Pernicious Anaemia, aiming to create awareness of the condition and potentially improve patient experiences. All the answers will remain completely confidential and will only be used by the research team. If you wish to withdraw from the research at any time you may do so with no further consequence. This survey will take approximately 20 minutes to complete.

Consent to take part in the research project

Yes, I consent to participate in the research study

Demographics

Please provide information regarding the following

1. Age

2. Gender

3. Nationality

4. Occupation/ profession

5. Postcode

Family History of Pernicious Anaemia (PA)

6. Do you have family history of PA?

Yes

No

If "yes", please specify.

Symptoms (pre-diagnosis)

This section refers to your symptoms before you were diagnosed with PA. Please try to answer these questions to the best of your knowledge.

7. What symptoms did you experience and how often?

	Always	Almost always	To a considerable degree	Occasionally	Seldom
Shortness of breath	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Extreme tiredness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Poor concentration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Confusion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mood swings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pins and needles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sleeping problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lethargy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unusual gait	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please indicate any other symptom(s) experienced and the frequency of these(e.g.breathless,occasionally)

8. On a scale of 1-5, can you please indicate how severe were your symptoms?

	Not severe(1)	Mild(2)	Moderate(3)	Severe(4)	Very severe(5)
Shortness of breath	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Extreme tiredness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Poor concentration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Confusion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mood swings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pins and needles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sleeping problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lethargy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unusual gait	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please indicate any other symptom(s) experienced including the level of severity(e.g.lack of sleep, severe)

PA Treatment

The following questions relate to the treatment that you are currently taking to alleviate your PA symptoms. Please answer as accurately as possible. If any of these questions do not apply to you please just answer "No".

9. Are you being treated for PA?

Yes

No

If "no", why?

10. What kind of treatment are you receiving? How often? Please provide details.

11. Did you start treatment following PA diagnosis?

Yes

No

If "no", why?

12. Have you ever had a break or discontinued treatment?

Yes

No

If "yes" ,please explain

13. Did you ever request for more frequent treatment?

Yes

No

If "yes" , why? And what was the outcome of your request?

14. Did you ever get over - the - counter treatment?

Yes

No

If "yes",why?

15. Do you feel that the treatment is working? How? Please explain.

16. If no, why not?

Symptoms post-diagnosis

This section refers to your symptoms after the PA diagnosis. Please answer the following questions as accurately as possible. If any of these do not apply to you please just answer "No".

17. What symptoms do you experience as a result of PA? How often?

	Always	Almost always	To a considerable degree	Occasionally	Seldom
Shortness of breath	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Extreme tiredness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Poor concentration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Confusion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mood Swings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pins and Needles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sleeping problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lethargy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unusual gait	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please indicate any other symptom(s) experienced and the frequency of these

18. On a scale of 1-5, can you please indicate how severe are your symptoms?

	Not severe(1)	Mild(2)	Moderate(3)	Severe(4)	Very severe(5)
Shortness of breath	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dizziness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Extreme tiredness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Poor concentration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Confusion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mood swings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pins and needles	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sleeping problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lethargy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Unusual gait	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please indicate any other symptom(s) experienced including the level of severity

19. How do you cope with your symptoms? Please explain.

20. Do you feel better since being diagnosed with PA?

Yes

No

If "Yes", can you please give details?

21. If "no", please give details.

22. How do you perceive this change? Please explain.

23. Do you feel that you can control your symptoms?

Yes

No

If "Yes", can you please explain how?

Co-Morbidities

This section refers to other conditions that you may have in addition to PA. Please answer to the best of your knowledge. If any of these do not apply to you please just answer "No".

24. Do you have any other conditions besides PA?

Yes

No

If "Yes", please provide details

25. Do you think that any of these conditions are associated with PA?

Yes

No

If "Yes", in what way?

PA impact on daily life

The following questions refer to the impact of PA on your daily life. If any of these do not apply to you please just answer "No".

26. Would you say that PA impacts on your daily life?

Yes

No

If "Yes", how?

27. Are there any limitations that you experience as a result of having PA?

Yes

No

If "Yes" , what kind of limitations?

28. Do you feel that you can deal with PA on a daily basis?

Yes

No

If 'no' why do you feel this way?

Health Services

This section refers to the provision of Health services in terms of dealing with your condition and providing adequate support. Please answer these questions to the best of your knowledge.

29. When diagnosed with PA, did you feel that you were informed by your GP regarding the condition?

Yes

No

If "No", would you have wanted to be informed?

30. Was this information beneficial for you?

Yes

No

N/A

If "No", why?

31. Did you look for information elsewhere?

Yes

No

If you have answered "yes" to the previous question, where did you look for information? Please give details. If you have answered "no", why not?

32. How often do you visit your GP regarding PA? Please specify.

33. In your opinion, what is the purpose of your visits to your GP?

- PA review
- Test monitoring
- Treatment

Other (please specify)

34 .Do you feel that you are able to discuss with your GP about any concerns that you may have regarding

PA?

- Yes
- No

If "no" , why not?

35. On a scale of 0-10, how helpful do you think that Health Services have been in dealing with your condition?

Not at all
Helpful (0)

Very
helpful (10)

A horizontal scale from 0 to 10. It consists of a light gray bar with 11 white circular markers spaced evenly along it. The markers are numbered 0 to 10 from left to right.

36. In your opinion, how could your doctor/ health services improve the help they give you?

THIS IS THE END OF THE SURVEY. THANK YOU VERY MUCH FOR YOUR TIME.

Study 4

Appendix 4.1 – Gp surgeries brief

THE RESEARCH TEAM

My name is Lenira Semedo and I am based at the University of South Wales, Treforest. The proposed study is part of an educational project (PhD) in collaboration with the departments of Haematology (Dr. Vinod Devalia) and Health Psychology (Dr. Linda Speck; Ms. Michele Williams) in the ABMU Local Health Board and The University of South Wales Health Psychology Research Group (Dr. Bev John; Dr. Faulkner; Dr. Gareth Roderique-Davies).

AIM PA is a severe chronic condition that poses serious implications for sufferers and medical management. This research group has already conducted an audit of patient's records (GP surgery) as well as interviews and a survey assessing the experience of living with PA in members of the Pernicious Anaemia Society. There is a lack of objective tests to assess B₁₂ status (Devalia, Hamilton & Molloy, 2014; Hooper, 2012; Pacholok & Stuart, 2011; Devalia, 2006). Furthermore, patients vary in their responses to B₁₂ therapy with no demonstrated physical benefit from more frequent treatment. In the absence of physiological parameters of patient's experience, it is crucial to consider patient-reported outcomes to evaluate how individuals make sense of their overall illness experience and how this may be related to the variability in treatment response. The key aim of the present study is to develop a patient-centred outcome measure for the identification and management of Health Related Quality of Life (HRQOL) for patients suffering from B₁₂ deficiency/Pernicious Anaemia. This tool will be subject to extensive testing to establish validity and reliability. The development of this tool will benefit patients as it will potentially enable clinicians to select treatment strategies according to individual patient needs which may reduce diagnostic delay, symptom severity and illness progression. Further benefits may accrue to GP's and NHS medical practitioners in terms of the reduction in both the frequency and length of consultations, as a consequence of the outcome measure and the improved adjustment of patients.

RECRUITMENT This research team aims to conduct a multi-centre study by recruiting patients from several GP surgeries within the ABMU area. The Ethics Research Proposal regarding this study is at the process of being submitted; however, ensuring the access to patients once Ethics is granted is paramount. The proposed procedure process will involve the administration of psychological measures including illness perceptions, coping strategies, locus of control and quality of life. We will require help from each GP surgery participating in this research in identifying patients with B₁₂ deficiency/PA who take B₁₂ injections. Then, a postal survey will be sent out to these patients with a covering letter from the surgery, the patient information sheet and informed consent attached in a pre-paid envelope (provided by the Sponsor: University of South Wales).

However, this may be discussed in terms of finding the best procedure for the recruitment process, in line with the requirements of each individual surgery, as to minimise disruption within each surgery by strictly following ethical guidelines when accessing vulnerable individuals.

The collaboration with Riverside would be invaluable for both patients suffering from PA/B₁₂ deficiency as well as health professionals.

CONSIDERATIONS When considering research that may potentially enhance patients' experiences and subsequent quality of life, one must consider patients' expectations of improved health services. Therefore, it will be made plain to participants that the research being carried out aims to further understand the experience of PA sufferers and that their participation in research is crucial to aid this understanding. Further, findings from this research may potentially inform decisions of service improvement from a patient's perspective.

RESEARCH DISSEMINATION The research team is prepared to engage with the practice administration team as well as GPs in case there is a need to further discuss the research study. The research team is also willing to disseminate the outcome of the research study at audit sessions/ GP monthly meetings.

In case you need any specialist input please contact Dr. Vinod Devalia (Consultant Haematologist; Telephone n.02088692742; E-mail: Vinod.Devalia@nhs.net)

I am looking forward to meet you, Kind Regards, Lenira Semedo

Appendix 4.2 – Faculty Ethics approvals

Dear Lenira,

Re: Investigating illness severity and health related quality of life in patients diagnosed with Pernicious Anaemia

I am pleased to report that your application for ethical approval has now been approved by the Faculty Ethics Sub Group.

Please note if you intend on deviating from the approved protocol or documentation you will need to request approval for any changes. I've attached the documents that are approved.

BW, Jon

*Jonathan Sinfield,
Research Governance Officer,
Research and Innovation Services (RISe) / Gwasanaethau Ymchwil ac Arloesedd,
Research and Business Development Office / Swyddfa Datblygu Busnes ac Ymchwil,
University of South Wales / Prifysgol De Cymru.*

Dear Lenira,

Re: Investigating illness severity and health-related quality of life in patients diagnosed with Pernicious Anaemia (FESG1702)

I am pleased to report that on the 20 February 2017 your low risk application for ethical approval was approved via chairs action.

Please note this approval is valid for 2 years from the date of issue. Upon the expiration of this approval you may apply for an extension of ethical approval. If you intend on deviating from the approved protocol or documentation you will need to request approval for any changes. I've attached the documents that are approved.

BW, Jon

*Jonathan Sinfield,
Research Governance Officer,
Research and Innovation Services (RISe)
Research and Business Development Office
University of South Wales*

Appendix 4.3 – NHS Ethics approval



North West - Lancaster Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 020 71048008

05 August 2016

Dr. Bev John

University of South Wales

Faculty of Life Sciences and Education

Trefforest, Pontypridd

CF371DL

Dear Dr. John

Study title: **Developing a patient-centred outcome measure for the identification and management of health related quality of life in patients suffering with Pernicious Anaemia**

REC reference: **16/NW/0582**

Protocol number: **N/A**

IRAS project ID: **181272**

Thank you for responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study. The revised documentation has been reviewed and approved by the sub-committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Approved documents

The documents reviewed and approved by the Committee are:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [Advert (phase 2)]	Version 0.2	01 August 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance indemnity]		
Letters of invitation to participant [Surgery letter template(phase 1)]	0.2	03 May 2016
Letters of invitation to participant [Surgery letter reminder template(phase 1)]	0.2	03 May 2016
Other [Provisional opinion response]	Version 0.1	02 August 2016
Other [clarification on access to medical records]		03 August 2016
Participant consent form [Consent form(phase 1)]	Version 0.2	01 August 2016
Participant information sheet (PIS) [Participant Information Sheet (phase 1)]	Version 0.4	01 August 2016
Participant information sheet (PIS) [Participant information sheet and consent form(phase 2)]	Version 0.2	01 August 2016
REC Application Form [REC_Form_18072016]		18 July 2016
Research protocol or project proposal [Protocol]	V1	14 November 2012
Summary CV for Chief Investigator (CI) [CV]		
Summary CV for student [Student CV]		
Summary CV for supervisor (student research) [CV]		
Validated questionnaire [Survey]		

With the Committee's best wishes for the success of this project.

Yours sincerely,



pp.

Dr Lisa Booth Chair

Appendix 4.4 – ABMU Health Board (R&D approval)



Bwrdd Iechyd Prifysgol
Abertawe Bro Morgannwg
University Health Board



Dyddiad/Date: 14th October 2016

ABMU Health Board Research & Development
Swansea University

Miss Lenira Semedo

Floor 1, Institute of Life Science 2

PhD (Health Psychology)

Singleton Park

University of South Wales

Swansea

Faculty of Life Sciences and Education

SA2 8PP

Treforest

☐☐01792 530888

Pontypridd

☐☐abm.rd@wales.nhs.uk

CF371DL

Dear Miss Semedo,

Re: Developing a patient-centred outcome measure for PA patients IRAS Ref: 181272 Sponsor: University of South Wales

Thank you for submitting the above named research proposal to ABMU Health Board for NHS R&D permission. The attached listed documents were reviewed.

Health Board R&D Governance checks have been completed and passed. Please accept this letter as confirmation of local NHS R&D Health Board permission.

May I take this opportunity to wish you well in undertaking the research. We will write to you in the future to request updates on the progress of the research and look forward to receiving outcomes of the study.

Yours sincerely,

PP 

Professor JW Stephens
Deputy Assistant Medical Director (R&D)

Re: Developing a patient-centred outcome measure for PA patients IRAS Ref: 181272 Sponsor: University of South Wales

Application Documents Received

Document:	Subtitle:	Version:
Evidence of insurance or indemnity (non-NHS sponsors only)	Insurance Certificate Expiry 31.07.2017	
Other (please specify)	Confirmation of protocol review email	
Research participant consent form - local version	Consent Form 01.08.2016	v0.2
Other (please specify)	Advert 01.08.2016	v0.2
REC favourable opinion letter and all correspondence	Validation Letter	19 Jul 2016
REC favourable opinion letter and all correspondence	Favourable Opinion with Additional Conditions	05 Aug 2016
Research protocol		v1.0, 14 Nov 2012
Summary CV for Chief Investigator (CI)	B John	
Site-Specific Information form checklist	ABM UHB	
Summary CV for Principal Investigator (PI)	L J M Speck	
Summary CV for local researchers and research nurses	V Devalia	
Summary CV for local researchers and research nurses	M Gray	
Other (please specify)	E-mail evidence ABMU	23 Aug 2016
Summary CV for student (signed/authorised copy)	L Semedo	
R&D Form (Parts A-D) (signed/authorised pdf or hard copy)		13 Sep 2016
Site-Specific Information Form (signed/authorised pdf or hard copy)	ABM UHB	16 Aug 2016
Research participant information sheet (PIS)		v0.4, 01 Aug 2016
Research participant information sheet (PIS)	PIS/ICF - Phase 2 (via Survey Monkey)	v0.2, 01 Aug 2016
R&D Application checklist		
Summary CV for Academic Supervisor	S Faulkner	07 Jan 2015

Evidence of insurance or indemnity (non-NHS sponsors only)	Employers' Liability & Public And Products Liability - 31 Jul 2016	15 Jul 2016
Other (please specify)	Reminder Letter to Potential Participants	v0.2, 03 May 2016
Letters of invitation to participant		v0.2, 03 May 2016
Validated questionnaire	Pernicious Anaemia Survey	

Appendix 4.5 – Advert for recruiting online participants

PERNICIOUS ANAEMIA PARTICIPANTS WANTED

We are a research team from the University of South Wales conducting a research study to investigate illness severity and health-related quality of life in patients diagnosed with Pernicious Anaemia (PA). The information provided in this study will aim to support tailoring treatment to individual needs.

If you have been **diagnosed with Pernicious Anaemia** by a health professional, if you are **receiving regular B₁₂ injections**, **if you are not taking part in this study via your GP surgery** and if you are **≥18 years old**, we would really appreciate your contribution to this research in order to develop a better PA understanding.

The present research has received ethical approval from the University of South Wales. Taking part in this study is voluntary, and all information provided by you will be confidential and anonymous.

If you would like to participate, please follow the link below and answer the questionnaire to the best of your knowledge.

Survey link: https://www.surveymonkey.co.uk/r/PA_HRQoL

Thank you very much

The research team

In case you have any queries please contact the researcher

(lenira.semedo@southwales.ac.uk)

Appendix 4.6 – Participant information sheet and consent form for online population

Phase 1 information and consent (via Survey Monkey)

Investigating illness severity and health-related quality of life in patients suffering with Pernicious Anaemia

Welcome and thank you for considering taking part in this research study. You are invited to participate in this research study because you have a diagnosis of Pernicious Anaemia (PA) and you receive regular B₁₂ injections to alleviate your symptoms. This study is part of an educational project (PhD) with the University of South Wales in collaboration with the Abertawe Bro Morgannwg NHS Trust. The North West-Lancaster Research Ethics Committee and the University of South Wales Faculty Ethics Sub Group have approved this study.

Before you provide your consent to participate or not it is important for you to understand the purpose of this research and what it will involve. Please take time to read this information carefully and discuss it with others if you wish.

The purpose of the present study is to investigate the impact of PA on health-related quality of life. This study aims to further knowledge concerning PA. The information provided by you may help improve future treatment and care of people diagnosed with PA.

By taking part you will be required to provide information regarding how PA is affecting your daily life, how you deal with your symptoms and how treatment is working for you.

Your participation in this study is voluntary. It is completely up to you whether or not to participate. Either way, you will not be penalized.

This survey will take approximately 30 minutes to complete. Please answer this survey to the best of your ability.

All your answers will remain completely anonymous. Data generated from this study will only be accessed by the research team and the study findings may be disseminated through peer-reviewed journals, presentations at conferences or other professional forums. In any publication, your individual contribution cannot be identified.

Once the study has ended, a summary of the findings will be available from the website were you accessed this survey.

Since there is no way of identifying your individual contribution you may not be able to withdraw your responses if you have exited the survey. In case you wish to erase your responses you will need to backtrack through the survey before you exit the same.

Disclosing health related information may cause distress for some individuals. If you perceive yourself to be in this situation, please contact the director of studies Dr. Bev John (bev.john@southwales.ac.uk; telephone n. 01443 654145).

If you wish to complain about this research you may do so with no further consequences. Please contact the research governance officer Jonathan Sinfield (jonathan.sinfield@southwales.ac.uk; telephone n.01443 484518).

After reading the information above you are encouraged to contact the researcher Lenira Semedo regarding any queries regarding the research study (lenira.semedo@southwales.ac.uk; telephone n. 01443 484517).

Before you provide your consent to participate in this study please confirm your diagnosis by a health professional, that you are receiving regular B₁₂ injections and that you are not currently taking part in this study through your local GP practice.

I can confirm that I have been diagnosed with Pernicious Anaemia by a health professional, I receive regular B₁₂ injections and I am not currently taking part in this study through my local GP practice.

Clicking on the "agree" button below indicates that:

- I have read and understood the above information. I have had the opportunity to consider the information, ask questions and have had these clarified to my satisfaction.
- I voluntarily agree to participate in the study
- I am at least 18 years of age
- 'I consent to the processing of my personal information for the purposes of this research study. I understand that such information will be treated as confidential and handled in accordance with the Data Protection Act 1998'
- I agree to my anonymised data being used in study specific reports and subsequent articles that will appear in academic journals

I agree to take part in this study

If you do not wish to participate in this research study, please decline participation by clicking on the "disagree" button.

I disagree to take part in this study

Appendix 4.7– Participant information sheet for clinical population



PARTICIPANT INFORMATION SHEET

Investigating illness severity and health related quality of life in patients diagnosed with Pernicious Anaemia

You are invited to take part in this research study because you have a diagnosis of B₁₂ deficiency/Pernicious Anaemia and you receive regular B₁₂ injections to alleviate your symptoms. This study is part of an educational project (PhD) in the University of South Wales in collaboration with the Abertawe Bro Morgannwg NHS trust.

Before you decide whether to participate or not it is important to you to understand the purpose of this research and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

The purpose of the present study is to investigate the impact of Pernicious Anaemia severity on quality of life. We want to know how Pernicious anaemia is affecting your daily life, how do you deal with your symptoms and how treatment is working for you.

This study aims to further knowledge concerning Pernicious Anaemia. The information provided by you may help improve future treatment and care of people diagnosed with Pernicious Anaemia.

The participation in this study is voluntary. It is completely up to you whether or not you participate. Either way, it will not affect the standard of care you currently receive.

Please take time to consider your participation and if you agree to participate in this study, please sign the enclosed consent form.

By participating, you also have the right to withdraw from the study at any time without providing a reason. In case you wish to withdraw, your data will be removed from the study.

Disclosing health related information may cause distress for some individuals. If you perceive yourself to be in this situation please contact the director of studies Dr. Bev John (Bev.john@southwales.ac.uk; telephone n. 01443654145).

This study involves filling up a survey regarding your Pernicious Anaemia experience. The survey will take approximately 30 minutes to complete. In case you have any issues completing this survey please contact the researcher (contact details available on the back of this form). After completion you are required to return it in the post with the consent form by using the pre-paid envelope provided to you.

Any information provided by you will be kept confidential and anonymous. If you provide your consent to participate we are planning to publish the results in peer-reviewed journals, presentation at conferences or other professional forums. In any publication, information will be provided in such a way that your individual contribution cannot be identified.

Once the study has come to an end, a summary of the findings will be available from your surgery website as well as the Pernicious Anaemia website. In case you don't have access to a computer and you are interested in a summary of the study findings, paper copies will be available to collect from your surgery.

In case you don't have access to a computer, would you like a paper copy of the summary of the study findings to be available to collect from your surgery?

Please circle the word that applies to your choice YES NO

After reading this information you are encouraged to ask or to contact the researcher regarding any queries about the research study.

In case you wish to complain about the present research you may do so, with no further consequences. Please contact Dr. Bev John (bev.john@southwales.ac.uk; telephone n.01443654145)

Thank you very much for taking the time to consider your participation in this study. If you wish to take part, please sign the attached consent form. This information is for you to keep.

Alternatively, if you do not wish to take to take part please sign and date below and post this form as well as the information pack in the pre-paid enveloped provided to you.

I do not wish to participate in this research study

Signature: ----- Date: -----

The researcher

Lenira Semedo (lenira.semedo@southwales.ac.uk; Telephone n: 01443 484 517

Appendix 4.8 – Consent form

(Form to be on headed paper)

Centre Number:

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Investigating illness severity and health related quality of life in patients diagnosed with Pernicious Anaemia

Name of Researcher: Lenira Semedo

Please initial box

1. I confirm that I have read the information sheet dated 5th April 2016 (version.0.3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
3. (If appropriate) I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from [company name], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. (If appropriate) I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.
5. (If appropriate) I agree to my General Practitioner being informed of my participation in the study.
6. (If appropriate) I understand that the information held and maintained by the Health and Social Care Information Centre and other central UK NHS bodies may be used to help contact me or provide information about my health status.
7. I agree to take part in the above study.

Name of Participant Date Signature

Name of Person Date Signature

Appendix 4.9 – GP letter template

	Surgery logo
	Address
	Contact
	Long date letter merged
	NHS Number
Title Calling Name Surname	
Home Full Address (stacked)	
Dear Title Surname,	
We are writing to you on behalf of Lenira Semedo (University of South Wales) who is conducting a research study investigating illness severity and health related quality of life in patients diagnosed with PA/B ₁₂ deficiency. As care providers, we are involved in treating our patients and promoting research that may advance knowledge on medical conditions.	
It is important for you to know that this letter is not to tell you to join this study. It is your decision. Your participation is voluntary. Whether or not you participate in this study will have no impact on the care you currently receive.	
Please review the enclosed information and take time to consider your participation. In case you wish to participate please fill in the attached questionnaire and the consent form and post it back to the surgery in the pre-paid envelope enclosed with this letter.	
If you are not interested in the study please circle your option in the attached information sheet and post the information pack back to the surgery in the pre-paid envelope provided to you.	
Thank you for your time and consideration.	
Sincerely,	

Appendix 4.10 – GP Reminder letter template

	Surgery logo
	Address
	Contact
	Long date letter merged
	NHS Number
Title Calling Name Surname	
Home Full Address (stacked)	
Dear Title Surname,	
We have recently contacted you to provide you with information regarding Pernicious Anaemia/B ₁₂ deficiency research being carried out by Lenira Semedo in the University of South Wales.	
We are contacting you again because we haven't yet received the questionnaire pack. If you wish to participate in this research please fill in the questionnaire and sign the consent form that was sent to you in the previous letter.	
If you do not wish to participate, please circle your option in the information sheet previously sent to you and post the information pack back to the surgery in the pre-paid envelope that was provided to you in the previous letter.	
You will not receive any more letters from the surgery regarding this research.	
In case you have any queries regarding this research, please contact the researcher (Lenira Semedo; lenira.semedo@southwales.ac.uk ; telephone n: 01443 484 517).	
Thank you for your time and consideration.	
Sincerely,	

Appendix 4.11 – Support letter from the PAS



Level 4, Brackla House, Brackla Street,

BRIDGEND CF31 1BZ

Tel. +44 (0)1656 769717

18/1/17

Dear Lenira,

Re. Research Project:

Investigating illness severity and health-related quality of life in patients suffering with PA.

I'm delighted that this society fully supports the above study and I confirm that we are happy for our members to access the study through the Pernicious Anaemia Society's website and via our network of local Support Groups.

I am also pleased to confirm that the Pernicious Anaemia Society agrees to offer support to any participant in the study should they experience any discomfort from disclosing health-related information to members of the research team as a consequence of participating in the above study.

All of us at the Pernicious Anaemia Society wish you well with your project.

Yours sincerely

Martyn Hooper MBE

Chairman

Appendix 4.12 – Survey



PERNICIOUS ANAEMIA SURVEY

Investigating illness severity and health related quality of life in patients diagnosed with B₁₂ deficiency/Pernicious Anaemia

Subject ID:

Date ___/___/___

Thank you for taking part in this survey. It aims to create a better understanding of B₁₂ deficiency /Pernicious Anaemia (PA) and potentially improve PA management from a patient's perspective. Therefore, ensuring that your views are represented is paramount. Please answer this survey to the best of your ability. All the answers will remain completely confidential and will only be used by the research team. If you wish to withdraw from the research at any time you may do so and this will not affect the quality of care you currently receive. This survey will take approximately 30 minutes to complete.

Before you begin, we would like you to answer a few general questions about yourself and your PA experience, by ticking the option that best applies to you or by filling in the space provided.

1. DEMOGRAPHICS

1.1 What is your age?

1.2 What is your gender?

- Male
- Female
- Other, please specify

1.3 What is your ethnic group?

White

- Welsh/English/Scottish/Northern Irish/British
- Irish
- Gipsy or Irish Traveller
- Any other White background, please describe

Mixed/ Multiple ethnic groups

- White and Black Caribbean
- White and Black African
- White and Asian
- Any other Mixed/ Multiple ethnic background, please describe

Asian/Asian British

- Indian
- Pakistani
- Bangladeshi
- Chinese
- Any other Asian background, please describe

Black/African/ Caribbean/ Black British

- African
- Caribbean
- Any other Black/African/ Caribbean background, please describe

Other ethnic group

- Arab
- Any other ethnic group, please describe

1.4 What is your postcode?

1.5 What is your current marital status?

- Single
- Living as married
- Married
- Civil partnership
- Separated
- Divorced
- Widowed

1.6 What is the highest degree or level of school you have completed? If currently enrolled, mark the previous grade or highest degree received.

- GCSE's/O levels
- A-levels
- Further education
- Higher Education

1.7 What is your employment status?

- Employed
- Self-employed
- Not currently employed
- Retired
- Unable to work
- Other

2. B₁₂ DEFICIENCY/PA RELATED INFORMATION

2.1 What is your diagnosis?

- B₁₂ deficiency
- PA

2.2 Do you have a family history of B₁₂ deficiency/PA?

- Yes
- No
- Not sure

2.3 How many years ago were you diagnosed with B₁₂ deficiency/PA?

2.4 Where was this diagnosis made?

- GP surgery
- Outpatient clinic
- Inpatient
- Other, please specify

2.5 Can you please provide details of the testing undertaken to achieve the diagnosis?

2.6 How often do you receive B₁₂ treatment?

- Every 3 months
- Every 2 months
- Every 6 weeks
- Every month
- Other, please specify

2.7 Have you ever requested for more frequent B₁₂ treatment?

- No
- Yes
- If 'yes' what was the outcome of the request?

2.8 Do you supplement your B₁₂ treatment?

No

Yes

If 'yes' please specify by including the type of supplementation and where do you get it from

2.9 Have you ever discontinued treatment?

No

Yes

If 'yes', why?

2.10 Are you a member of any support organisation to help you deal with PA?

No

Yes

If 'yes' please specify

2.11 Have you been diagnosed with another chronic condition besides PA?

No

Yes

If 'yes', please specify

Appendix 4.13 BRIEF-COPE (FORM A)

These items deal with ways you have been coping with your condition. There are many ways to try to deal with problems. These items ask what you have been doing to cope with the fact you that suffer from B₁₂ deficiency/ PA. Obviously, different people deal with things in different ways, but we are interested in how you have tried to deal with it. Each item says something about a particular way of coping. We want to know to what extent you have been doing what the item says. How much or how frequently. Don't answer on the basis of whether it seems to be working or not—just whether or not you are doing it. Use these response choices by ticking the item that applies to you. Make your answers as true FOR YOU as you can.

1.	I've been turning to work or other activities to take my mind off things.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
2.	I've been concentrating my efforts on doing something about the situation I'm in.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
3.	I've been saying to myself "this isn't real."	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
4.	I've been using alcohol or other drugs to make myself feel better.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
5.	I've been getting emotional support from others.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
6.	I've been giving up trying to deal with it.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
7.	I've been taking action to try to make the situation better.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
8.	I've been refusing to believe that it has happened.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
9.	I've been saying things to let my unpleasant feelings escape.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
10.	I've been getting help and advice from other people.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot

11.	I've been using alcohol or other drugs to help me get through it.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
12.	I've been trying to see it in a different light, to make it seem more positive.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
13.	I've been criticizing myself.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
14.	I've been trying to come up with a strategy about what to do.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
15.	I've been getting comfort and understanding from someone.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
16.	I've been giving up the attempt to cope.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
17.	I've been looking for something good in what is happening.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
18.	I've been making jokes about it.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
19.	I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
20.	I've been accepting the reality of the fact that it has happened.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
21.	I've been expressing my negative feelings.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
22.	I've been trying to find comfort in my religion or spiritual beliefs.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
23.	I've been trying to get advice or help from other people about what to do.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
24.	I've been learning to live with it.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
25.	I've been thinking hard about what steps to take.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot

26.	I've been blaming myself for things that happened.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
27.	I've been praying or meditating.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot
28.	I've been making fun of the situation.	I haven't been doing this at all	I've been doing this a little bit	I've been doing this a medium amount	I've been doing this a lot

Appendix 4.14 The multidimensional health locus of control scale (FORM B)

Instructions: Each item below is a belief statement about your B₁₂ deficiency/PA with which you may agree or disagree. Beside each statement is a scale which ranges from strongly disagree (1) to strongly agree (6). For each item, we would like you to circle the number that represents the extent to which you agree or disagree with that statement. The more you agree with a statement, the higher will be the number you circle. The more you disagree with a statement, the lower will be the number you circle. Please make sure that you answer **EVERY ITEM** and that you circle **ONLY ONE** number per item. This is a measure of your personal beliefs; obviously, there are no right or wrong answers.

1=STRONGLY DISAGREE (SD)	4=SLIGHTLY AGREE (A)
2=MODERATELY DISAGREE (MD)	5=MODERATELY AGREE (MA)
3=SLIGHTLY DISAGREE (D)	6=STRONGLY AGREE (SA)

	SD	M D	D	A	M A	SA
1 If I get sick, it is my own behaviour which determines how soon I get well again.	1	2	3	4	5	6
2 No matter what I do, if I am going to get sick, I will get sick.	1	2	3	4	5	6
3 Having regular contact with my physician is the best way for me to avoid illness.	1	2	3	4	5	6
4 Most things that affect my health happen to me by accident.	1	2	3	4	5	6
5 Whenever I don't feel well, I should consult a medically trained professional.	1	2	3	4	5	6
6 I am in control of my health.	1	2	3	4	5	6
7 My family has a lot to do with my becoming sick or staying healthy.	1	2	3	4	5	6
8 When I get sick, I am to blame.	1	2	3	4	5	6
9 Luck plays a big part in determining how soon I will recover from an illness.	1	2	3	4	5	6
10 Health professionals control my health.	1	2	3	4	5	6
11 My good health is largely a matter of good fortune.	1	2	3	4	5	6
12 The main thing which affects my health is what I myself do.	1	2	3	4	5	6
13 If I take care of myself, I can avoid illness.	1	2	3	4	5	6
14 Whenever I recover from an illness, it's usually because other people (for example, doctors, nurses, family, friends) have been taking good care of me.	1	2	3	4	5	6
15 No matter what I do, I'm likely to get sick.	1	2	3	4	5	6
16 If it's meant to be, I will stay healthy.	1	2	3	4	5	6
17 If I take the right actions, I can stay healthy.	1	2	3	4	5	6
18 Regarding my health, I can only do what my doctor tells me to do.	1	2	3	4	5	6

Appendix 4.15 Somatic symptom scale (FORM C)

Instructions: Your answers to the following questionnaire will help in understanding problems that you may have. Please answer every question to the best of your ability by putting a cross in the answer that applies to you.

During the past 4 weeks, how much have you been bothered by any of the following problems?	Not bothered	Bothered a little	Bothered a lot
1.Stomach pain			
2.Back pain			
3. Pain in your arms, legs or joints (knees, hips, etc.)			
4.Feeling tired or having little energy			
5.Trouble falling or staying asleep or sleeping too much			
6.Menstrual cramps or other problems with your periods(Women only)			
7.Pain or problems during sexual intercourse			
8.Headaches			
9.Chest pain			
10.Dizziness			
11.Fainting spells			
12.Feeling your heart pound or race			
13.Shortness of breath			
14.Constipation, loose bowels or diarrhoea			
15.Nausea, gas or indigestion			

Appendix 4.16 The Brief Illness Perception Questionnaire (FORM D)

For the following questions, please circle the number that best corresponds to your views in relation to your B₁₂ deficiency/PA:

How much does your illness affect your life?										
0	1	2	3	4	5	6	7	8	9	10
no affect										severely
at all										affects my life
How long do you think your illness will continue?										
0	1	2	3	4	5	6	7	8	9	10
a very										forever
short time										
How much control do you feel you have over your illness?										
0	1	2	3	4	5	6	7	8	9	10
absolutely										extreme amount
no control										of control
How much do you think your treatment can help your illness?										
0	1	2	3	4	5	6	7	8	9	10
not at all										extremely
										helpful
How much do you experience symptoms from your illness?										
0	1	2	3	4	5	6	7	8	9	10
no symptoms										many severe
at all										symptoms

How concerned are you about your illness?											
0		1	2	3	4	5	6	7	8	9	10
not at all											extremely
concerned											concerned
How well do you feel you understand your illness?											
0		1	2	3	4	5	6	7	8	9	10
don't											understand
understand											very clearly
at all											
0		1	2	3	4	5	6	7	8	9	10
not at all											extremely
affected											affected
emotionally											emotionally
Please list in rank-order the three most important factors that you believe <u>caused your illness</u> .											
<i>The most important causes for me:-</i>											
1. _____											
2. _____											
3. _____											

Appendix 4.17 The Hospital Anxiety and Depression Scale (FORM E)

Emotions play an important part in most illnesses. Being aware of these feelings may help you more when dealing with your B₁₂ deficiency/PA. Read each item and underline the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought out response.

1.	I feel tense or 'wound up'	Most of the time	A lot of the time	From time to time, occasionally	Not at all
2.	I still enjoy the things I used to enjoy	Definitely as much	Not quite so much	Only a little	Hardly at all
3.	I get a sort of frightened feeling as if something awful is about to happen	Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all
4.	I can laugh and see the funny side of things	As much as I always could	Not quite so much now	Definitely not so much now	Not at all
5.	Worrying thoughts go through my mind	A great deal of the time	A lot of the time	From time to time but not too often	Only occasionally
6.	I feel cheerful	Not at all	Not often	Sometimes	Most of the time
7.	I can seat at ease and feel relaxed	Definitely	Usually	Not often	Not at all
8.	I feel as if I am slowed down	Nearly all the time	Very often	Sometimes	Not at all
9.	I get a sort of frightened feeling like 'butterflies' in the stomach	Not at all	Occasionally	Quite often	Very often
10.	I have lost interest in my appearance	Definitely	I don't take so much care as I should	I may not take as much care	I take just as much care as ever
11.	I feel restless as if I have to be on the move	Very much indeed	Quite a lot	not very much	Not at all
12.	I look forward with enjoyment to things	As much as I ever did	Rather less than I used to	Definitely less than I used to	Hardly at all
13.	I get sudden feelings of panic	Very often indeed	Quite often	Not very often	Not at all
14.	I can enjoy a good book or radio or TV programme	Often	Sometimes	Not often	Very seldom

Appendix 4.18 WHOQOL-BREF (FORM F)

The following questions ask how you feel about your quality of life, health, or other areas of your life. **Please answer all the questions.** If you are unsure about which response to give to a question, **Please choose the answer that appears most appropriate**, this can often be your first response. Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks**. **Please read each question, assess your feelings, and circle the number that accurately reflects your answer.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you got enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5
20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to **how often** you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Thank you very much for your time. We would appreciate you to check that this survey is fully completed.

Before you finish is there anything that you would like to add?
