

The psychological profile of children with immune thrombocytopenia and the  
factors influencing well-being

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## Abstract

Immune thrombocytopenia is a blood disorder, characterised by low platelet count, bleeding and bruising. In children, symptoms are generally mild and spontaneous remission is common. Literature relating to other paediatric conditions is reviewed and considered alongside limited studies with adults and children with ITP which suggest that their life is affected by the condition. A holistic approach to treatment should be adopted which is informed by the psychological profile of ITP.

The current study used questionnaires completed by children with ITP and their parents attending haematology outpatient appointments. Questionnaires assessed adjustment variables of emotional and behavioural functioning, fatigue, quality of life, and executive functioning. A measure was created to explore the effect of subjective appraisal from parents and children on the other investigated variables.

In total, 37 families took part. Results showed most children in the sample did not have significant difficulties. However, parents' ratings of children on a measure of total psychological difficulties, and specifically on emotional symptoms, were higher for this sample compared with children without ITP. Fatigue as rated by parents and children was on average higher for children with ITP compared with children without ITP. For a proportion of children (20%), ratings on the Global Executive Composite and the Behaviour Regulation Index indicated some difficulty with executive functioning, though these results should be viewed with caution given the sample size and other limitations of the study. Severity ratings of the condition varied between parent, child and clinician. Bleeding severity and platelet count generally did

not correlate with other measures. Some appraisal measures were significantly associated with adjustment variables.

Possible explanations for the findings are discussed. Results are then considered relative to the Risk and Resistance model (Wallander & Varni, 1992). Despite limitations, this study provides important information that contributes to knowledge about the profile of ITP as well as the inter-relationship between factors that affect well-being in paediatric conditions more broadly.

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## **1. Introduction**

### **1.1 Overview**

Chronic physical health conditions can have significant effects on individuals' psychological well being (Barlow & Ellard, 2006; Varni, Limbers, & Burwinkle, 2007). The World Health Organisation defines health as a multidimensional construct including social and emotional components as well as physical aspects (WHO, 1946). In order to provide optimal care as healthcare providers, we need to understand the holistic presentation of a condition, including both the medical and psychosocial characteristics (Department of Health, 2005).

There are some similarities with regard to the psychosocial impact of different types of physical health conditions (Stein & Jessop, 1982), such as effects of treatments, being perceived as different due to the condition, or disruption to a person's daily routine. However, it has also proved useful to study the impact of specific conditions, to determine unique effects. This thesis looks at immune thrombocytopenia (ITP), a bleeding disorder, in children and the specific issues presented for this condition. The risk and resistance model as described by Wallander and Varni (1992) is outlined as a model for understanding how psychological, contextual and clinical aspects of a condition might interact together, including in ITP.

This thesis explored emotional and behavioural functioning, fatigue, executive functioning and quality of life in children affected by ITP. These

variables were selected as there is extensive literature to suggest these are significant factors affected in children with a range of chronic health conditions, as discussed in each section below. Additionally, these aspects have been reported or observed by clinicians in paediatric haematology clinics for children with ITP, but, as yet, have not been explored in research studies. These variables are initially discussed in relation to physical health conditions, including those that might be most similar to ITP in children. The literature relating to each of these aspects of functioning in adults and children with ITP is covered, highlighting gaps in the literature. The potential role of cognitive appraisal of the condition, as highlighted in the risk and resistance model (Wallander & Varni, 1992), is also discussed. Finally, an outline of the current study is given; this study aimed to address omissions in previous research and establish the profile of fatigue, executive functioning and emotional-behavioural outcomes for children with ITP, as well as the inter-relationships between these variables.

## **1.2 Impact of chronic childhood health conditions**

This chapter outlines evidence to suggest that the presence of a chronic health condition is a risk factor for poor outcome in different adjustment domains. Children with physical disorders may be at risk of general adjustment problems (Barlow & Ellard, 2006), poor psychological well-being (Lavigne, & Faier-Routman, 1992) and reduced quality of life (Varni, Limbers, & Burwinkle, 2007). Differences in outcomes are seen across conditions (Lavigne & Faier-Routman, 1992). Specifically in blood disorders,

poorer outcomes have been shown for those with sickle cell anaemia (Anie, 2005), Von Willibrands disease (Barr et al, 2003), and coagulation disorders as a group (Taulikar, Shadbolt, McDonald, & Pidcock, 2006) compared with the general child population.

ITP is another blood disorder that has received recent research interest, particularly around understanding the secondary (psychosocial) characteristics of the condition. Investigating ITP would not only tell us more about ITP, but also provide information that may help identify aspects common to other disorders and isolate those unique to ITP, thus informing us more generally about outcomes in chronic conditions and blood disorders.

### **1.3 Immune Thrombocytopenia (ITP)**

Immune thrombocytopenia (ITP) is a rare blood condition, with an estimated incidence in children between 1.9 and 6.4 per 100,000 children per year (Terrell et al., 2010). The condition is characterised by low blood platelet counts, bleeding (e.g., nosebleeds) and bruising. Haemoglobin and white cell counts are typically normal (unless as a consequence of significant bleeding) (Bannon & Carter, 2007). Diagnosis is based on clinical history, physical examination and blood counts but it remains a diagnosis of exclusion (Bannon & Carter, 2007); for ITP to be diagnosed, other conditions must be considered and ruled out. This includes more serious diseases such as leukaemia or congenital blood problems (Bannon &

Carter, 2007), and this is likely to cause anxiety for families whilst these diagnoses are under consideration.

The terms 'immune', or 'idiopathic', thrombocytopenia identifies the condition as occurring independent of other conditions, and the disease is thought to be a dysfunction in the body's immune system, incorrectly attacking its own cells (Blanchette & Bolton-Maggs, 2010). The condition affects equal numbers of boys and girls, although at younger ages there are slightly more boys with the condition (Kühne et al., 2001). In children, symptoms are often mild, although there is a very small risk of internal bleeding and, in particular, intracranial haemorrhages which can be life-threatening (Blanchette & Bolton-Maggs, 2010). ITP should not impact on a child's ability to engage with most age-expected activities, although they may be advised, particularly in the initial stages of an illness, to avoid activities which are at high risk for head injury or internal trauma (Bannon & Carter, 2007).

In children with ITP, spontaneous remission is common (Neunert et al., 2013). Chronic ITP in children is defined as lasting longer than 12 months and occurs for 15-20% of children with ITP (Bannon & Carter, 2007). Treatment options include, among others, intravenous immunoglobulin, splenectomy and steroids (Blanchette & Bolton-Maggs, 2010). Decision to treat ITP is largely based on clinical factors, such as bleeding severity. However, due to good spontaneous remission rate in children and the risks



associated with treatments, a 'watch-and-wait' approach is usually adopted (Blanchette & Bolton-Maggs, 2010), meaning that active treatment is withheld unless clinical risk reaches a certain level. Blood tests are carried out routinely to monitor the condition. However, in line with the World Health Organisation's holistic definition of health (WHO, 1946), clinicians also need to consider all aspects of a child's presentation, and adopt a biopsychosocial assessment of a child's needs. It has been suggested that a range of factors, including bleeding symptoms and quality of life should be considered in treatment decisions for ITP (Buchanan & Adix, 2001).

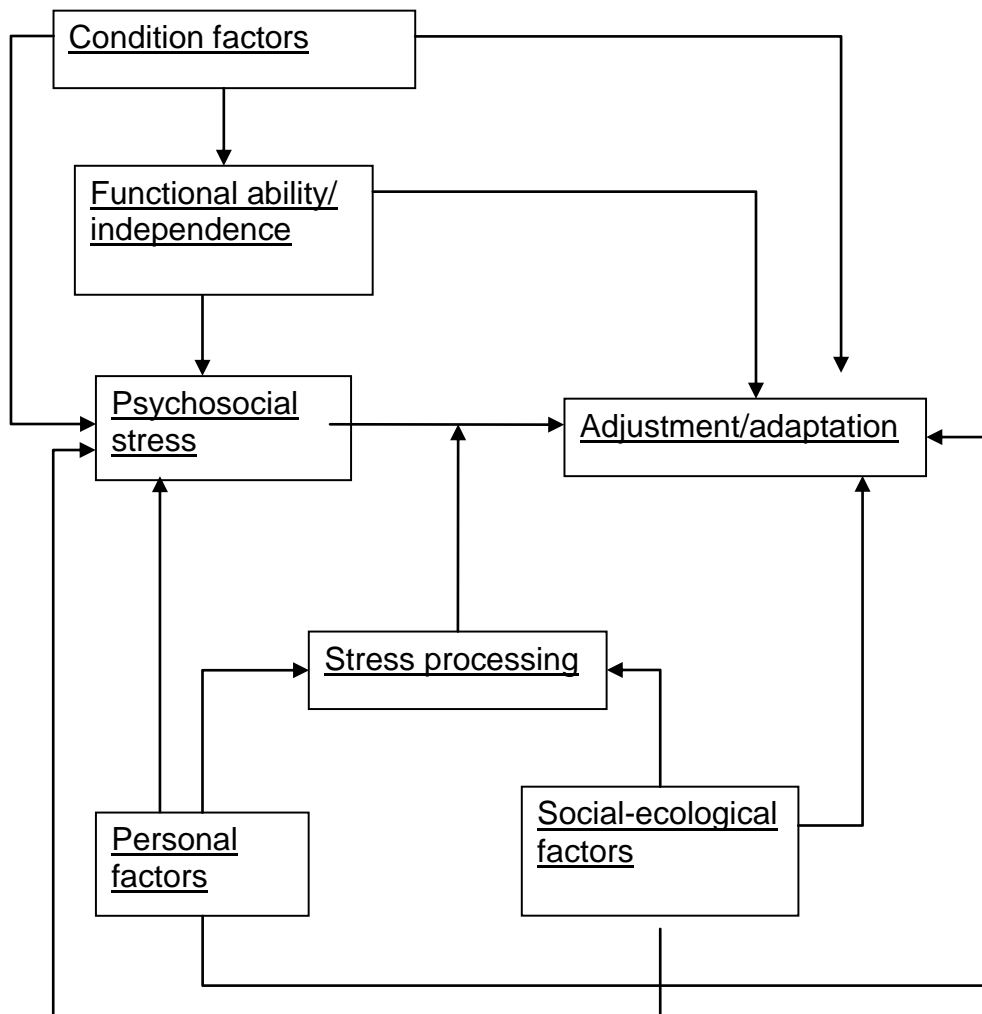
As a chronic condition, ITP may have features common to other health conditions. At present, the psychosocial components of ITP are understudied, so this thesis draws on literature for other physical health conditions, including other non-malignant blood disorders, such as sickle cell anaemia and haemophilia. These make a good comparison to ITP as they also require regular blood tests and hospital appointments and involve a degree of uncertainty about the course of the illness. However, treatment of ITP is more conservative than these two comparison conditions and on the whole it is usually considered to be less severe (Bannon & Carter, 2007). Furthermore, it may be hypothesised that there are unique features of ITP that contribute to variability in adjustment, including the visibility of the condition through bruising and bleeding, the particular uncertainty associated with the 'watch-and-wait' treatment approach, potential emotions such as anxiety or even guilt due to its unknown cause/aetiology, the

confusion of multiple treatment options and the approach to restricting physical activity. Research into the well-being and quality of life for children with ITP has begun but other more specific areas of psychosocial functioning have not been investigated.

#### **1.4 Risk and Resistance Model**

Although having a chronic health condition may be a risk factor for poor outcomes, researchers have suggested that it may be that an interplay of a range of factors determines outcome, and this may explain why only certain individuals experience difficulties. Wallander and Varni (1992) developed the risk and resistance model, also known as the disability-stress model, for understanding the impact of disability and illness (Figure 1). Although not tested in this study, the model is described here in order to provide a theoretical framework for understanding the findings of the study.

Figure 1: Risk and Resistance Model (taken from Wallander & Varni, 1992)



The model was developed from a background of literature that showed that there is wide individual variation in adjustment to a chronic health condition, which cannot be accounted for by presence of the condition alone (Wallander & Varni, 1992). For instance, Wallander, Varni, Babani, Banis, and Wilcox (1988) found significant variation in maternal reports of externalising behaviour problems and social competence, as measured on the Child Behaviour Checklist (Achenbach & Edelbrock, 1983), for children

with chronic health conditions, suggesting that other factors must have an impact on outcomes. Analysis showed that variation occurred dependent on condition, gender and situational variables, such as family income. Similarly, in a population-based survey of 17,110 families (Adams & Hardy, 1989), whilst 31% of children were reported to have chronic physical health conditions, only a small proportion of these experienced problems or significant impact on their lives (Newacheck & Taylor, 1992). In this study, there was significant heterogeneity in the type of conditions surveyed, including allergies. The impact on children and young people may be different for more severe and enduring conditions, or those requiring hospital treatments.

The model shown in Figure 1 proposes that there are risk and resistance factors that contribute to outcome and adjustment. The authors proposed that risk factors are those elements that contribute to a poor outcome; resistance factors provide some protection against poor outcome (Wallander & Varni, 1992). Due to the complexity of the model, often only sections of the model and selected pathways have been tested in any given study. Although a brief description of some of the key findings are discussed below in order to illustrate the relevance of this model to this particular research study, a review of full the evidence base for the model is beyond the scope of this thesis.

Risk factors include illness parameters, such as overall condition severity, specific symptoms and the illness's visibility, functional (in)dependence, and ongoing daily stress, which may or may not be associated with the illness itself. There are mixed results on the link between the severity of the illness and outcome (Billings, Moos, Miller, & Gottlieb, 1987; Casey, Brown & Bakeman, 2000). To explain this, the model suggests that specific disease factors may have both direct and indirect effects on outcome. For instance, severity has been shown to be associated with stress (Casey et al., 2000) and both stress related to the illness (Casey et al., 2000, LeBovidge, Lavigne & Miller, 2005) and general life stresses (Coker et al., 2011) have been found to affect psychological adjustment outcome for children. Similarly, pain (as a condition risk factor) has been shown to be directly related to a child's adjustment, for instance mood outcome (Gil et al., 2003). However, pain may also limit the amount of activity that a child can engage with, indicating an indirect route for symptoms of a condition to impact on outcome (Gil et al., 2003). Functional independence is suggested in the model to mediate the relationship between condition variables and outcome, and poorer emotional outcome is indeed observed in paediatric populations with cancer with worse functional ability (Varni, Katz, Quiggins, & Friedman-Bender, 1996, as cited by Wallander & Varni, 1998).

'Resistance factors', including intrapersonal, socio-ecological and stress processing generally attenuate the effect of risk factor variables in both a direct and indirect way, and therefore lead to better outcome (Wallander &

Varni, 1998). Stress processing encompasses cognitive appraisal and was influenced by the work of Lazarus and Folkman (1984), who suggest that it is the perception of an event or situation that influences outcome rather than the nature of the event itself. In support of this, Varni and Setoguchi (1996) found no association between objective measures of limb loss and perceived physical appearance but more positive perceived physical appearance was related to lower depressive symptoms. Walker and colleagues (Walker, Smith, Garber, & Claar, 2007) found that in children with chronic abdominal pain, appraisal of daily stressors was significantly associated with adjustment, as measured by depressive ratings and somatic symptoms. Illness appraisal is discussed further later in the chapter. The model suggests that a person's ability and style in processing stress is influenced by personal attributes (including age, gender, and personality factors), a finding which has been verified in numerous studies (e.g., Mak, Blewitt, & Heaven, 2004). Other sociological and contextual factors such as social economic factors and family background (Drotar, 1997; Karlson et al., 2012; Wagner et al., 2003) have been shown to influence outcome, directly and through their effects on appraisal. However, discussion of these factors is beyond the scope of this thesis. For further evidence and discussion see Wallander and Varni (1998).

Though the authors did not originally specify what 'adjustment outcome' referred to, research has since used behavioural, emotional and quality of life measures as discussed below. As each area of adjustment is explored,

the literature on the impact of personal factors (age and gender) and condition factors will be briefly discussed where literature is available. For ITP, the main illness factors discussed are bleeding severity and platelet count and these are discussed in relation to the different outcome variables where research exists.

The risk and resistance model (Wallander & Varni, 1992) does have limitations and in particular it has been criticised for incorrectly specifying moderating and mediating variables (Holmbeck, 1997). Also, the model describes a clear separation between risk and resistance factors, but it has been suggested that many factors could function as both, for example where high values of a factor (e.g., use of active coping methods) could result in positive outcome but low scores result in negative outcome (Olsson, 2008). Nevertheless, Wallander and Varni (1992) emphasised that mapping out variables that affect outcome would help develop intervention and prevention programs to support individuals and families to manage and adjust to chronic conditions.

Due to the complexity of the model and the design and scope of this study, the model was not explored and tested in relation to ITP. Rather, the primary aim of this study was to explore a range of adjustment outcomes, not previously investigated for ITP and the model provided a framework to consider how these outcomes may interact with each other and contribute to variation in outcome. This study aimed to include a wider exploration of

adjustment outcomes in ITP, whereas previously research has focused on clinical outcome and more recently quality of life only. After various adjustment outcomes have been discussed, the role of cognitive appraisal in relation to ITP is covered and then a suggested risk and resistance model for ITP is presented.

## **1.5 Psychological adjustment**

### **1.5.1 Behavioural problems**

Behavioural problems have been used as a measure of adjustment in the risk and resistance model for chronic illnesses (Wallander & Varni, 1998). When referring to behaviour problems, this thesis is referring to externally observable behaviours by the child or young person that have a negative effect on the environment around them (Eisenberg et al., 2001). Scales to assess behaviour or conduct problems have items that cover hitting out or fighting with others, destroying things, and disobedient behaviour (e.g., Achenbach & Edelbrock, 1983; Goodman, 1997). As some scales also include tantrums, there may be some overlap with emotional difficulties and the display of these. The discussion of the literature below does not include observable problematic habitual behaviours such as nail biting or bed-wetting.



***Behavioural problems: general health conditions.***

Chronic health conditions have been shown to be associated with behavioural problems, for instance as measured by the externalising subscale of the Child Behaviour Checklist (Achenbach & Edelbrock, 1983; Piquart & Shen, 2011) and using bespoke measures (Gortmaker, Walker, Weitzman, & Sobol, 1990). Piquart and Shen's meta-analysis (2011) compared data across many different studies. The analysis included 569 studies involving 51,422 child participants, with 1,897 children with sickle cell disease. As the researchers did not limit the analysis to studies published in English, this meta-analysis also provides cross-cultural data. They found increased levels of externalising behaviours overall, a finding that was observed in the studies of children with sickle cell. Across conditions, increased behaviour problems were particularly reported by parent compared to child ratings, with adolescent ratings having the smallest effect size. A significant effect for gender was found, with higher reported externalising problems in studies with a majority of males in the sample. This finding does parallel similar patterns found in normal populations (Leadbeater, Kuperminc, Blatt, & Hertzog, 1999). In the meta-analysis, studies were only included if they had used the Child Behaviour Checklist (Achenbach & Edelbrock, 1983). However, this scale has been criticised for use with physical conditions due to the overlap between the somatic complaints subscale and characteristics of the illness itself (Perrin, Stein, & Drotar, 1991).

The only blood disorder in the meta-analysis above was sickle cell disease. There is some evidence of behaviour problems in haemophilia (Evans, Cottrell & Shiach, 2000), although most studies show behavioural functioning within the normal range (Trzepacz, Vannatta, Davies, Stehbins & Noll, 2003). However, even in conditions identified as 'benign', behavioural problems have been reported. For instance, in studies of benign epilepsy, parents rated their children as having significantly higher rates of behavioural problems compared with norms (Connolly et al., 2006) or matched controls (Weglage, Demsky, Pietsch, & Kurlemann, 1997). Most children will outgrow this form of epilepsy in childhood (Peters, Camfield, & Camfield, 2001) and in this way it is similar to the pattern of recovery found in childhood ITP.

### ***Behavioural issues in ITP.***

Exploration of behavioural issues in ITP is extremely limited. However, we might expect a similar behavioural adjustment profile in ITP to other physical health conditions. Although ITP may be considered less severe than sickle cell disease (Bannon & Carter, 2007) discussed above, parents do report problem behaviours in some other benign conditions (Connolly et al., 2006).

In studies involving adults with ITP, patients reported problems with mood swings and anger (Mathias et al., 2008), largely related to steroid treatment. In the study, the extent to which these problems were externalised was not explored, nor were any potential effects of gender. For children and young

people, anger and mood changes may present as conduct or behavioural problems, but as yet this has not been investigated for those with ITP. Anecdotal reports from clinicians indicate that families report problems with behaviour in children with ITP (K. Sibson, personal communication, February 4, 2014), beyond those who may be experiencing effects from steroid treatments (Suarez, Rademaker, Hasson, & Mangogna, 1986) and that these may have a significant impact on a child's well-being, participation in daily life, social contact, academic functioning. Research needs to examine the prevalence of these problems, compared with normative scores, and the extent to which this may be associated with other psychosocial characteristics of the condition. In particular, emotional difficulties and problems with conduct are often observed together in children with chronic health conditions (Pinquart & Shen, 2011).

### **1.5.2 Mood and emotional symptoms**

Mood or emotional symptoms have also frequently been used as a measure of adjustment for children with health conditions. 'Emotional symptoms' or 'emotional functioning' as discussed here encompasses low mood/depression and anxiety as measures often combine these factors. Where attempts have been made to measure depression and anxiety separately, this is made clear. (Emotional functioning as described here does not refer to the ability of children and young people to recognise and appropriately respond to emotions.)

***Mood and emotional symptoms: general health conditions.***

Using large samples from several studies, Varni, Limbers and Burwinkle (2007) found that self-reported 'emotional functioning' was significantly lower for children with chronic health conditions than a healthy control group. However, emotional functioning was based on a brief subscale of a wider quality of life measure, which may bring into question the construct validity of this measure. In a different meta-analysis in which studies did use specific measures of emotional functioning and depression, depressive symptoms were worse in children with chronic physical conditions (Pinquart & Shen, 2011), although there was large variation across conditions, emphasising the importance of measuring the impact on emotional wellbeing for individual conditions. Most relevant to the current study, other blood disorders such as sickle cell are associated with depressive symptoms in children (Yang, Cepeda, Price, Shah, & Mankad, 1994).

It is important to note that particular treatments such as steroids can have an impact on mood (Stuart, Segal, & Keady, 2005). Also, in one study (Mrakotsky et al., 2013) exploring psychological symptoms in children with inflammatory bowel conditions, sleep mediated the effect of steroids on depressive scores so treatment effects may also be influenced by other factors. Furthermore, how an illness is perceived has been shown to have an effect on mood. That is, a more positive appraisal is correlated with

better emotional outcome (Lewis & Kliewer, 1996). This will be discussed further in the section below on illness appraisal.

***Mood and emotional symptoms: ITP.***

Through focus groups consisting of 15 adults in total, 93% of people with ITP (14 adults) expressed issues related to emotional health (Mathias et al., 2008), including depressive symptoms such as low mood and loneliness, anxiety around consequences of the illness, and mood swings. This categorisation was broad and these are descriptive results since the study did not include a quantitative measure of emotional difficulties. In children with ITP, parents have reported emotional changes, specifically emotional lability, and further research in this area has been recommended (Freedman, Garvey, Elinder, & Blanchette, 1998). A possible biological mechanism for mood changes in ITP could be explained by the reduced level of platelets and their role in the transport and re-uptake of serotonin, a neurotransmitter involved in mood regulation (Berger, Gray & Roth, 2009). In a similar way to other paediatric conditions, and as described in the risk and resistance model (Wallander & Varni, 1992), cognitive appraisal and general understanding of ITP may impact on the emotions of this group but this has not been explored. Indeed, some authors have suggested that uncertainty around illness may exacerbate feelings of anxiety or distress (Hoff, Mullins, Chaney, Hartman, & Domek, 2002; Ingerski et. al., 2010). It has been suggested that there needs to be investigation into how mood disorders may interact with other characteristics, such as fatigue in children

with ITP (Newton et al. 2011; Zehnder et al., 2010), particularly as these factors have been hypothesised to effect each other for other chronic conditions (Hewlett et al., 2011). To date, there has been no study that has used standardised measures of mood or emotion for children with ITP.

### **1.5.3 Fatigue**

#### ***Definition and measurement issues.***

Fatigue is recognised as a subjective experience of tiredness and/or decreased energy, expressing itself in physical, social or emotional domains, which is persistent over time and distinctly abnormal (McCabe, 2009). Fatigue may be present in individuals with low mood, but mood and fatigue may also exert independent effects (Visser & Smets, 1998). Measures of fatigue, particularly in child populations, both with and without chronic physical health conditions, have been slow to develop and research of fatigue in children remains scarce (McCabe, 2009). Furthermore, studies that have examined fatigue in paediatric settings have often used proxy reports from parents or clinicians, which have shown a large discrepancy with child reports (Hinds et al., 1999). As fatigue is largely considered a subjective measure, it is vital to gain self-report in this domain. Varni and colleagues (Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002) have produced a measure that assesses fatigue in children as young as 5 years old, with adapted wording and use of smiley faces for responding. It is important to consider a wide range of ages as population surveys indicate that there may be differences in experience of fatigue between adolescents

and younger children (Jordan et al., 2000). It is important to establish the degree of fatigue in any condition as it may affect a child's functioning on several domains, such as cognitive functioning and school performance and ability to self-regulate, possibly having an impact on emotional functioning (Swain, 2000) as discussed above.

***Fatigue: general health conditions.***

Children report high levels of fatigue in a range of conditions, including cancer (Hicks, Bartholomew, Ward-Smith, & Hutto, 2003), multiple sclerosis (MacAllister et al., 2009), and sickle cell anaemia (Panepinto et al., 2014). Fatigue might be anticipated in conditions that affect bodily functioning in a severe way or conditions that require substantial chemotherapies, known to alter fatigue levels. However, it has been identified in other conditions. For instance, in systemic lupus erythematosus, an auto-immune disease with symptoms affecting the blood and skin, 67% of children identified problems with fatigue (Houghton, Tucker, Potts & Mckenzie, 2008). However it should be noted that this study used a relatively small sample size (n=15), and used a fatigue measure that has not been validated for children. This also meant that normative comparisons were not possible. Across a range of chronic conditions, the experience of fatigue is identified by children as an important symptom (Eddy & Cruz, 2007) and may affect general attitude toward illness (Iobst, Nabors, Brunner, & Precht, 2007). Fatigue has been associated with academic performance and mood, and could be a result of the condition itself, or of the treatment (McCabe, 2009).

Although in the general population there is a trend for girls to report more fatigue and be at risk for persistent severe fatigue (Viner et al., 2008), studies of fatigue in chronic conditions have not always explored gender differences. Using both parent and child reports may help to distinguish whether this is a gendered report bias or a difference in the presentation of fatigue for girls and boys. Also, many studies in chronic conditions have not asked younger age groups, despite measures being available.

***Fatigue: ITP.***

Mechanisms for fatigue in ITP are poorly understood (Zehnder et al., 2010) but possible contributors to fatigue may be restrictions in physical activity, worry and stress (Hill & Newland, 2015), insomnia related to corticosteroid treatment (Stuart et al., 2005) and, for a very small proportion of ITP patients, anaemia caused by excessive bleeding (Liebman & Pullarkat, 2011).

Through a literature review of 39 articles of adults with ITP and adult focus groups, Mathias et al. (2008) found various reports of fatigue. The focus groups were facilitated by a trained moderator using a semi-structured interview format, and two researchers analysed each transcript. Fatigue was mentioned by 14 out of 15 people (93%) in two focus groups, but not mentioned at all in a third group. One potential limitation of this study is that it was unclear if the researchers that conducted the literature search were



the same as analysed the transcripts, which may influence how themes were extracted.

In other adult ITP studies, using a generic quality of life measure, scores on an energy/vitality subscale have shown both significant (McMillan, Bussel, George, Lalla, & Nichol, 2008) and non-significant differences when compared with normal populations (Zhou et al., 2007). Of note, in the latter study, energy was significantly lower in adults with ITP of duration at least six months, compared with those with more acute ITP. This could indicate a cumulative effect of fatigue over time. In another study, 39% of UK adult respondents with ITP had significantly higher frequencies of fatigue and this was associated with reduced platelet count (Newton et al., 2011). The majority of participants in this study had chronic ITP; it is unclear whether this association between platelet count and fatigue would be observed in the acute stages. No measures of emotional functioning were used so it is unclear whether the concurrent effects of symptoms of depression were affecting fatigue levels. Indeed, the researchers recommend that these measures be used in future studies. It should also be noted that the results were obtained through questionnaires sent through ITP support associations, with a response rate of 31% (585 adults). Members of the associations and those that responded may not represent the whole ITP population. Whilst a greater percentage of women reported fatigue than men (41% of women versus 33% of men) this difference was not a statistically significant effect. Some researchers have suggested that different

physiological mechanisms, namely oxidative stress, may be different for men and women with ITP and this may have an impact on fatigue experiences (Kamhieh-Milz & Salama, 2014).

In children with ITP, there are descriptions of fatigue in the literature, confirmed in interviews with children, parents and clinicians (Barnard et al., 2003). A postal survey conducted through the UK-based ITP Support Association (Sarpatwari et al., 2010), found reports of fatigue in children, which 6-10% of children identified as contributing to them missing school. It should be noted that the 94 children that responded may have been a self-selecting group (that is, only those with the worst symptoms of ITP and fatigue may have responded). If participants were captured attending routine clinic appointments, some of this self-selection bias may be reduced. Reports of fatigue in children with ITP have also been found through review of clinical notes (Blatt, Weston, & Gold, 2010). In this instance, authors searched for reports of the symptoms in the notes and did not do any comparison with a different group of patients without ITP, making it difficult to establish the extent to which fatigue may be different for this group, compared with the normal population and other paediatric conditions. Apart from these accounts, no systematic investigation of fatigue has been conducted in children with ITP, including investigation of the link between fatigue and platelet count, similar to that conducted by Newton et al. (2011) for adults, or exploring gender differences or treatment effects. This lack of research is in line with a general dearth of literature for fatigue in children

(McCabe, 2009). As many children with ITP will not be receiving active treatment, it may be more possible to attribute fatigue to the condition itself.

#### **1.5.4 Executive functioning deficits**

Executive functioning is a set of abilities concerned with planning, initiation, organisation, self-monitoring and regulation (Elliott, 2003). Executive functioning may be associated with the three variables mentioned above (behaviour, mood and fatigue), or may mediate or moderate the impact of ITP on these variables.

Frustrations in struggling to think and process things may manifest in behavioural problems. In epilepsy, three years following onset of first seizure, executive function difficulties were a significant predictor for poorer behavioural outcomes (Baum et al., 2010). Also in a paediatric cancer group, executive functions, including working memory, cognitive flexibility, self-monitoring and behavioural inhibition, were all significantly correlated with behaviour problems (Campbell et al., 2009).

In adults it is established that mood disorders have an impact on executive functioning (Fleming, Blasey, & Schatzberg, 2004). There is limited investigation into the relationship between mood and executive functioning in children. On tests of executive functioning and problem solving, anxious-depressed boys (aged 9-11 years and with an absence of any physical illness) scored worse compared with controls from the same class

(Emerson, Mollete & Harrison, 2005). Conversely, lower executive functioning may influence mood through the effect on ability to cope with every day stresses, in stress perception and stress processing ability (Williams, Suchy, & Rau, 2009). However, in one study, in children with ADHD, cognitive inattentive symptoms explained less than 1% of variance in emotional lability (Sobanski et al., 2010).

One study of children with multiple sclerosis (MS), found that executive function, as measured by two neuropsychological tests, was significantly associated with cognitive fatigue (Goretti et al., 2012), although parent and child reports were associated with different tests. Unfortunately, this study does not describe when the reports of fatigue were requested. If these were given straight after a poorly performed test, this may have affected the ratings, with participants trying to justify or explain their performance through fatigue. This study compared scores to matched controls but there was little evidence to suggest that they had been matched on characteristics that would affect fatigue levels, apart from presence of significant illness or injury.

The link between fatigue and executive function is further supported by findings in patients with chronic fatigue, where switching attention and divided attention have both been found to be significantly different from the normative mean (Haig-Ferguson, Tucker, Eaton, Hunt, & Crawley, 2009). However, in MS and chronic fatigue syndrome, fatigue is likely to be

severely affected; it is unclear whether lower levels of fatigue may still have an impact on executive functioning. It is important to investigate executive function for its potential effect on other variables (behaviour, mood and fatigue) but it may also have other effects on a child's well-being and quality of life.

### ***Executive function in general health conditions***

In adults, there are several studies that document executive function deficits in particular physical illnesses (Schillerstrom, Horton, & Royall, 2005). In one study, 72% of adult (medical) inpatients performed poorly on bedside executive function tests (Schillerstrom, Deuter, Wyatt, Stern, & Royall, 2003). However, the situation of being in hospital may have an effect on executive functioning, independent of physical state. Although research is limited, several findings of executive function deficits have been reported for children with various blood disorders. Problems with inattention have been found in children with haemophilia through informant reports (Spencer, Wodrich, Schultz, Wagner, & Recht, 2009) and neuropsychological testing (Whitt et al., 1993). A particular strength of this latter study was that practitioners carrying out the testing were blind to the study objectives. In a meta-analysis review of neurocognitive profiles of children with sickle cell disease, 11 out of 13 studies found difficulties in executive functioning (Berkelhammer et al., 2007). Although impairments may be larger in those with infarcts (occlusion or haemorrhage in the brain), one study found that 13% of children without any evidence of silent infarct, which may be a closer

comparison to children with ITP, had deficits in executive function compared with 0% of healthy siblings (Schatz, Brown, Pascual, Hsu, & DeBaun, 2001). More recently, a study using neuropsychological tests found poorer performance on a test of planning and execution in children with sickle cell compared with healthy controls, matched for socioeconomic status (Hijmans, Fijnvandraat, et al., 2011). In this study, 79% had no history of stroke or observable vascular blockage, although silent infarcts were not examined. Beyond vascular injury (infarct), executive function may be affected by more general changes in blood flow and pressure, as deficits in executive function are present in children with hypertension, as reported by parents (Lande et al., 2009).

There is some evidence for steroid effects on executive function. For example, for younger child patients with cancer, during steroid treatment weeks, emotional control and behaviour regulation sub-scales of the Behaviour Rating Inventory of Executive Function, BRIEF (Gioia, Isquith, Guy & Kenworthy, 2000a) were significantly worse than off-steroid weeks (Mrakotsky et al., 2011). Similarly in inflammatory bowel disease, for children (aged 8-17 years) on steroid treatment, reports from children themselves and parents indicated problems with executive function, although these effects were modest and the effect of steroids on self-reported metacognition was not significant after controlling for disease severity (Mrakotsky et al., 2013). However, there is some evidence for

steroid effects on executive function so this should be considered in any study.

To date, exploration of executive function in chronic conditions has been limited. Many studies have used neuropsychological tests, which have been criticised for lower ecological validity (Anderson, 2002), as they are often conducted in settings that are quiet and controlled, and also increase the demand for child participants in research. As well as eliminating these disadvantages to neuropsychological testing, self and informant reports can draw on daily observation and experience over several weeks to give advantage over a single point in time investigation (Payne, Hyman, Shores, & North, 2011)

### ***Executive function in ITP.***

Generalised cognitive difficulties have been reported by adults with ITP (Frith, Watson, Maggs, & Newton, 2012) using a self-report measure (Cognitive Failures Questionnaire; Broadbent, Cooper, FitzGerald, & Parkes, 1982). Self-report could both overestimate cognitive difficulties, if the individual perceives the problem to be worse, or underestimate if individuals fail to remember how many errors they have made. The study found that cognitive problems were unrelated to platelet count and steroid use but were significantly related to fatigue.

Cognitive problems have been reported in children with ITP (Matoth, Zaizov, & Frankel, 1971) and reported anecdotally from haematology clinics (K. Sibson, personal communication, February 4, 2014) but have not been studied in detail or more rigorously. A recent review of the management for ITP calls for further research into the cognitive profile of patients with ITP (Cooper, 2014). Given the limitations in self-report and neuropsychological testing, reports from other sources may be useful to establish the extent of cognitive problems and reports from family members of children may be relevant and, as yet, have not been included in research.

Executive function, as a specific domain of cognition, has not been investigated in children or adults with ITP. Although intracranial haemorrhage in ITP is rare, it is possible that micro-bleeds that go undetected may be having an effect on cognitive function. Similar to other haematological conditions, executive function may still be affected in children with ITP, regardless of bleeding in the brain (Bannon & Carter, 2007). In addition, increased anxiety or low mood may have an impact on executive functions, as may activity levels (Diamond & Lee, 2011), or steroid use. Therefore there are several reasons why it is important to investigate the profile of executive functioning in children with ITP and the inter-relationships between executive function, mood and fatigue.



### **1.5.5 Quality of Life**

Quality of life (QoL) can be defined as a subjective assessment of the extent to which personal goals, standards and values have been met, and the achievement of a desirable life (Diener, 2006; World Health Organisation, [WHO], 1997). It is affected by a person's status, their relationships, and their environment (WHO, 1997). In the literature about chronic health conditions, the term health-related quality of life (HRQoL) has been used to focus on specific health-related elements affected by the condition. In recent years, there has been a growing emphasis on assessing quality of life in relation to a children's physical health (Varni, Limbers, & Burwinkle, 2007).

#### ***Quality of Life: Impact of chronic physical health conditions.***

Many studies have shown that having a chronic condition affects a child's quality of life (Ingerski et al., 2010; Varni et al., 2007). In one study of a range of different physical conditions, treatment, course of the illness (persistent or intermittent), length of diagnosis and severity all affected parent and child reports of child overall quality of life (Varni et al., 2007). However, this study did not include any haematological disorders, and the sample sizes meant that participants could not be demographically matched across conditions. In contrast, Miners et al. (1999) did not find any correlation between disease characteristics (specifically, bleeding frequency), and quality of life for those with haemophilia. In another review across seven different chronic conditions, including sickle cell disease, children's quality of life as reported by themselves and their parents, was

significantly worse than a healthy control group (Ingerski et al., 2010). This study found differences between conditions, which supports the importance of considering individual chronic illnesses as they may present unique and differential effects. This study controlled for demographic variables, which were significantly different across conditions, although it failed to control for other disease characteristics such as severity and length of diagnosis. Parent reports also indicate lower quality of life in children even for conditions identified as medically benign (Connolly et al., 2006).

The factors discussed above have been linked with quality of life for other health conditions. For instance, it has been shown that for children with epilepsy, mood and quality of life are related (Tracy, Dechant, Sperling, Cho, & Glosser, 2007) and that anxiety and depression may moderate the relationship between disease characteristics and quality of life in children with multiple sclerosis (MS) (Janssens et al., 2003). Significant correlations on formal measures have also been found between fatigue and quality of life in a sample of children with MS (MacAllister et al., 2009). A 2006 study (Connolly et al., 2006) found a significant correlation between lower cognitive function and reduced quality of life in epilepsy. The conceptual and methodological overlap of these concepts was considered throughout this current study.

### ***Quality of life: Impact of ITP.***

In a sample of 236 people over 14 years old with ITP, health related quality of life assessed using a generic quality of life measure was significantly lower on all domains compared with the normal population in China (Zhou et al., 2007). In this study, using a bespoke visual analogue measure, fear of bleeding was a significant predictor of reduced HRQoL. Reduced HRQoL in adults with ITP has also been found in an American study (McMillan et al., 2008).

ITP may affect a child's life in several ways. Some of these may be similar to other chronic conditions and include the disrupted routine and stress caused by hospital visits, the invasiveness and pain caused by medical procedures, the uncertainty around illness and the psychological impact of feeling different. More uniquely to ITP, it is possible that characteristics such as possible restrictions on physical activity, visible presentations of the illness (bleeding and bruising) and the 'watch-and-wait' treatment approach recommended in childhood ITP could be anticipated to affect a child's overall quality of life. For instance, in a questionnaire survey, children with ITP reported being bothered about the restrictions in their physical activities, and this was more so than for adults with the condition (Sarpawari et al., 2010).

Klaassen et al. (2013) found that quality of life measured using the Pediatric Quality of Life Inventory™ (Varni et al., 2002) was significantly lower in children with ITP, compared with values for a healthy population. In recent studies, it has been shown that quality of life, as measured with the Kids ITP tools (Klaassen et al., 2007), an ITP specific quality of life measure, is likely to differ between acute/newly diagnosed and chronic child ITP patients (Mokhtar, Farid, Shaker, & Farrag, 2014), and across the first six months of diagnosis (Heitink-Pollé et al., 2014; Strullu et al., 2013). The relationships between fatigue, executive functioning, emotional and behavioural functioning and quality of life have not been looked at for adults or children with ITP.

## **1.6 The role for illness appraisal**

It has been discussed that clinical aspects of a disease may impact on a person's well-being and adjustment. However, in a number of studies, disease characteristics alone do not explain the pattern and variation in adjustment and outcome. For instance, in sickle cell disease in children, disease characteristics, such as pain and clinical presentation, were found to be unrelated to quality of life ratings, suggesting there must be another process mediating adjustment (Anie, 2005). The risk and resistance model (Wallander & Varni, 1992) uses an umbrella term of 'stress processing', which incorporates cognitive appraisal as a possible mediating factor. Cognitive appraisal refers to the internalised representation and explanations of the illness. This aspect of the risk and resistance model is

supported by the authors' own research showing that subjective, and not objective, ratings of limb deficiencies influenced adjustment, as measured by depressive symptoms (Varni & Setoguchi, 1991). In a more recent study, when controlling statistically for certain disease characteristics, attitude toward illness was a significant predictor for depression and anxiety symptoms resulting from stress (LeBovidge et al., 2005). Another study demonstrated that both parent and adolescent attributions were related to adolescent adjustment (Guion & Mrug, 2012). Three aspects of appraisal (perceived severity, impact and ability to cope) will now be discussed.

#### **1.6.1 Illness appraisal: severity**

Due to inconsistent findings in the association between objective severity with illness characteristics, some researchers have suggested that use of perceived severity may be more appropriate (Barakat, Lash, Lutz, & Nicolaou, 2006). In children (aged 8-15 years) with chronic abdominal pain, perceived severity of daily stressors was a strong predictor of outcome (depressive symptoms, somatic complaints and functional ability) (Walker et al., 2007). Also, children were more likely to employ coping strategies when stressors were perceived as more severe. However, severity appraisal was a significant predictor of depressive and somatic outcomes even once coping had been controlled for through mediational analysis, indicating that the appraisal itself, regardless of subsequent action taken, is an important factor. Girls were significantly more likely than boys to appraise stressors as more severe. This study did not use any report from other sources or

objective measures to verify coping or condition presentation, so it is unclear how appraisals matched with objective measures of stress and whether coping strategies were employed as reported. In children who have recovered from cancer, the mother's appraisal of the threat severity of the illness contributed to child's anxiety and child's subjective ratings of the illness (Stuber et al., 1997). Therefore, it is important to investigate both child and parent ratings of severity to examine discrepancies between them and the specific effect of parent appraisals on child well-being. Few studies have used clinician subjective severity ratings for comparisons.

### **1.6.2 Illness appraisal- impact**

Another domain within illness appraisal is the perceived impact of the illness. This could be on the individual or the family and may include financial and social impact, and sense of mastery of condition management (Stein & Jessop, 2003). Alternative terms of burden and intrusiveness have been used to consider the impact of illness, and include the impact of the condition itself as well as related treatment impact or hospital visits. It has been suggested that an illness may be perceived as more intrusive when an individual feels like they have reduced control and if the illness is more severe (Devins, 2010). Illness intrusiveness has been shown to correlate with psychosocial outcomes in adults (Devins et al., 1983). For children with cancer, their ratings of increased burden as measured on a bespoke scale, correlated with lower scores of affect, including both low mood and worse anxiety (Currier, Hermes, & Phipps, 2009). The scale created had good

internal reliability, although did include items asking about impact on mood, which may be confounded with mood measures; they would be expected to be correlated. Parents' ratings of impact may also have an effect. In a study of parents of children with epilepsy higher impact ratings were associated with higher emotional, cognitive and behavioural problems and worse quality of life in children (Camfield, Breau & Camfield, 2001). Higher impact ratings were related to objective measures of severity and related to lower acceptability of the condition by parents.

### **1.6.3 Illness appraisal- ability to cope**

In addition to the perception of the illness, the person's perception of their ability to cope is also likely to be important. Lazarus and Folkman's model (1984) identified that it is the discrepancy between demands of a problem (primary appraisal) and perceived ability to cope with it (secondary appraisal) that determines adjustment outcome. Secondary appraisal or 'ability to cope' has often been termed self-efficacy. Self-efficacy has been linked with lower anxiety in chronic conditions (Dalhbeck & Lightsey, 2008), better quality of life for those with cancer (Cunningham, Lockwood & Cunningham, 1991), fewer self-reported condition-specific symptoms in those with diabetes (Griva, Myers, & Newman, 2000), and, in patients with sickle cell disease, fewer psychological problems (Clay & Telfair, 2007). Self-efficacy may be more concerned with the perceived ability to carry out certain illness related behaviours. As there is no significant aspect of self-management in ITP, the question becomes more "Can I cope emotionally

with this condition?” However, secondary appraisals such as these have not been extensively examined in chronic conditions and not in individuals with ITP.

In paediatric populations, children may particularly rely on others around them, namely their parents, for support. Therefore, parents’ ability to cope (or perceived ability to cope) may have a significant effect on child well-being. Indeed, for mothers of children with asthma, the mothers’ own perceived ability to cope was related to child’s quality of life (Sales, Fivush, & Teague, 2008). It may also be that child and parent appraisals influence each other (Guion & Mrug, 2012).

#### **1.6.4 Illness appraisal in ITP**

Similar to literature discussed above which has reported mixed findings on the link between severity of illness and adjustment outcome, Neunert et al. (2009) found no correlation between bleeding severity or platelet count with HRQoL in children with ITP. This was true for child and parent proxy reports and for acute and chronic ITP and suggests that, similar to other haematological conditions, it may be how the illness is appraised or perceived that has an effect on subjective well-being and outcomes. Although a common treatment approach is a ‘watch-and-wait’ approach, this may still have significant impact on the individual and family due to constant anxiety and regular hospital visits to monitor the condition. One ITP specific quality of life measure (Klaassen et al., 2007) does include questions about



what aspects 'bother' children with ITP, but no studies have been conducted into appraisal of ITP. Adults with ITP have reported differences with their clinician in the significance of symptoms of ITP and treatment side effects (Guidry, George, Vesely, Kennison, & Terrell, 2009) but no investigation has been conducted with children with ITP or their parents. Uncovering a discrepancy between clinician and patient ratings of severity or impact may highlight an area for intervention. Establishing whether objective disease characteristics or subjective experience of the illness is affecting outcome, will determine potential support strategies and psychological care for this patient group.

### **1.7 Summary**

Research studies have used several different outcome measures to investigate the effect of chronic health conditions on individuals. Research suggests that emotional and behavioural functioning, fatigue and cognitive functions may be affected. However, these domains have not yet been investigated for children with ITP. In a similar way to other physical health conditions and specifically blood disorders, and based on patterns seen in adults with ITP, differences in these domains would be expected for children with ITP. Issues unique to ITP (such as fluctuating platelet count) may exert specific effects. Although recent research in children with ITP has begun to look beyond clinical outcome, research so far has been limited to quality of life measures and there remains a gap in exploring other domains of outcome for this population, including psychological measures, and any

interaction of variables. Furthermore, the importance of the role of cognitive appraisal is discussed widely in the literature in regard to understanding adjustment to health conditions but as yet this has not been explored for children with ITP.

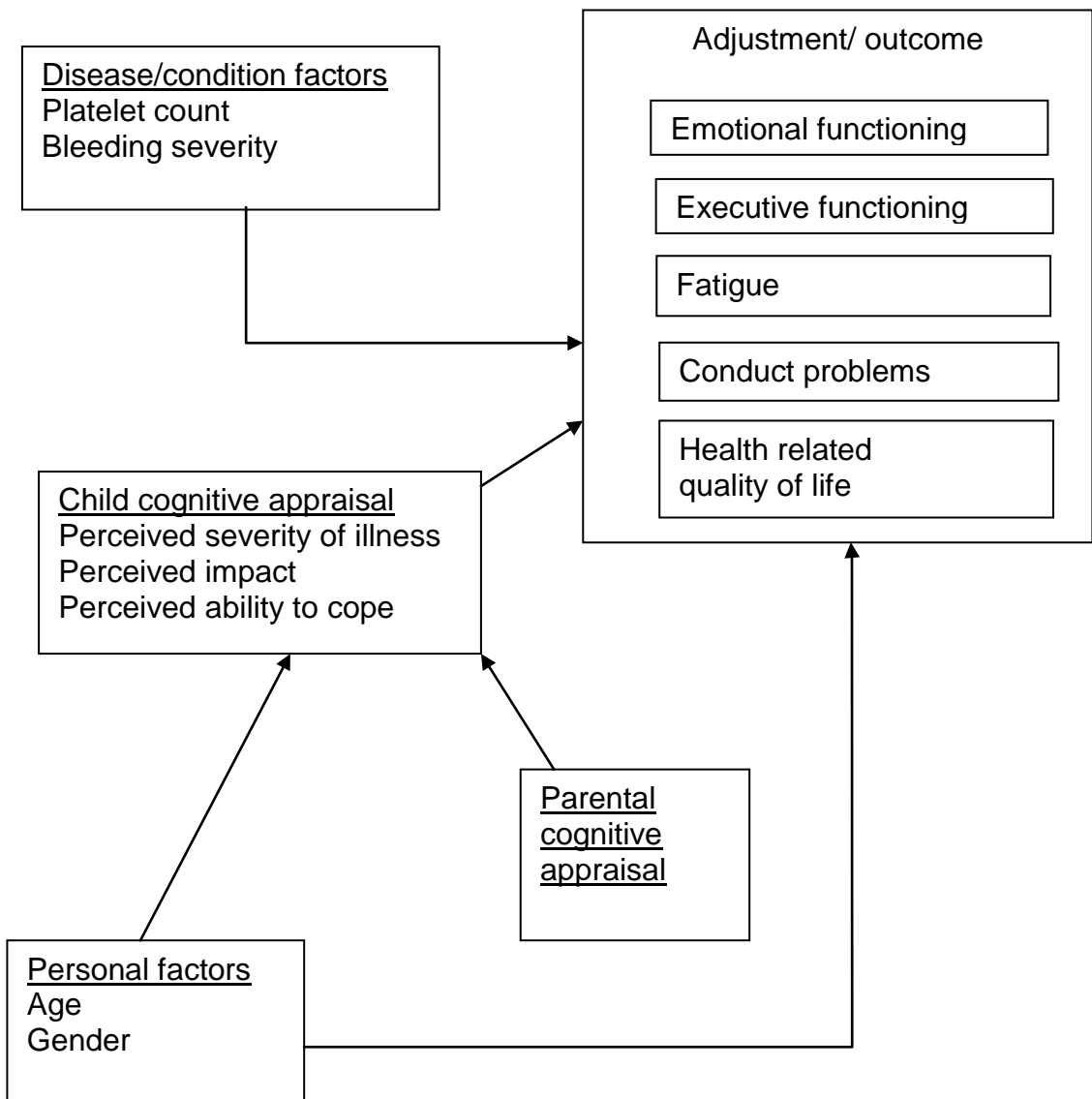
### **1.8 The Risk and Resistance Model as Applied to ITP**

It is important to have a theoretical framework to postulate how characteristics of the disease, the individual and outcome inter-relate. Here, the risk and resistance model (Wallander & Varni, 1992) has been adapted to show how factors might interact for children with ITP (Figure 2), taking into account the factors discussed above.

In this suggested adaptation, adjustment to ITP is conceived to include emotional and behavioural functioning, fatigue and quality of life because these were considered to be important areas of adjustment outcome identified in paediatric literature and the limited existing research in ITP. As discussed, these factors were thought to be inter-related. Cognitive functioning has been tentatively added here as a potential adjustment outcome. It could also be considered an aspect of the condition itself, although the underlying biological mechanism for this is unclear. Platelet count and bleeding severity have been included as clinical characteristics in the model as these are the current main markers for clinical outcome and treatment decision making in ITP. These were expected to correlate with adjustment outcome. In the original model, appraisal acts as a moderator

between stress and outcome. However, only direct associations between appraisal and outcome were explored in the current study.

Figure 2: Suggested Risk and Resistance Model for ITP, adapted from Wallander and Varni (1992)



Note. Only factors relevant to the current study have been included in the model

In addition, the association between parent and child appraisal was explored. Age and gender would be expected to influence adjustment outcome directly, as well as through different appraisal styles in boys and girls and the effect of different levels of understanding the condition dependent on the child's age.

### **1.9 Current study**

This study aimed to address significant gaps in the research literature relating to children with ITP, which would help develop the treatment and support for patients as well as add to our understanding of interaction patterns between clinical variables and psychosocial outcome for this and other paediatric conditions. This study investigated psychosocial problems in adjustment and quality of life for children with ITP and their parents. Children with ITP and their parents were approached through routine hospital appointments and asked to complete standardised questionnaires on levels of fatigue, emotional-behavioural functioning and health related quality of life. Parents completed a measure of executive functioning for their child, an area completely unexplored in ITP. Use of standardised measures allowed for comparisons with children with other physical conditions and those without any condition, whilst disorder specific measures were included in order to explore the unique characteristics of ITP. Children and parents were also asked their appraisal of the child's condition, in line with the suggested role of appraisals as suggested in Wallander and Varni's (1992) theoretical model.

The main aim of the research was to establish the psychological profile of children with ITP, and determine whether children with ITP have poor adjustment outcomes as measured by higher rates of emotional and behavioural problems, fatigue and executive function difficulties compared with the normal population. Exploratory analyses were made with sickle cell populations where this data was available. The study also investigated the associations between variables with brief exploration of the demographic variables. Finally, the study examined factors that were related to health related quality of life. The study did not test theoretical models but used the risk and resistance model (Wallander and Varni, 1992) as a framework to understand the findings.

The research questions were:

1. Would children with ITP would display poor levels of adjustment, including increased rates compared with the normal population for:
  - Emotional and behavioural problems?
  - Fatigue?
  - Executive functioning difficulties?
2. How would clinical measures (platelet count and bleeding severity) be associated with adjustment variables?
3. What would be the relationship between outcome adjustment variables?
4. Would more positive appraisal would be associated with better adjustment?

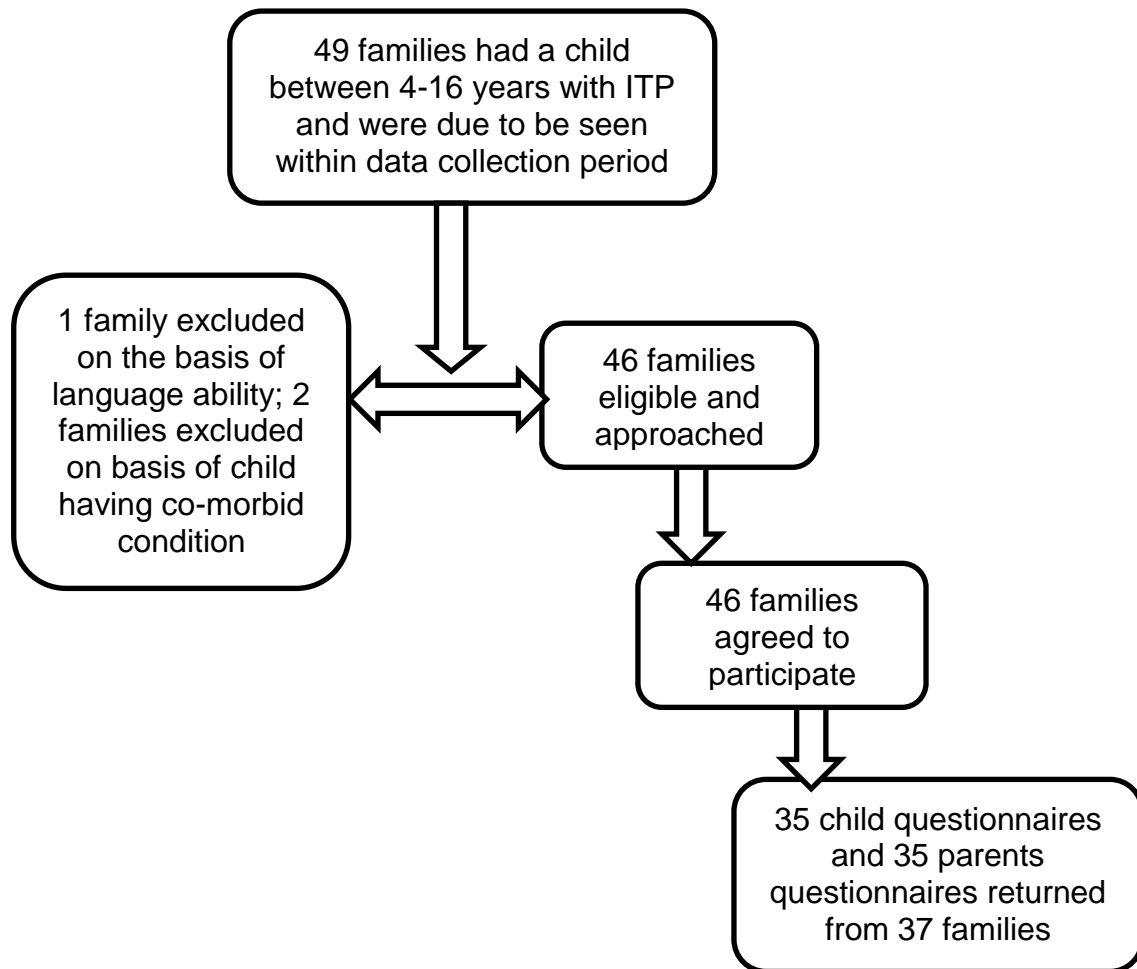
## **2 Method**

### **2.1 Participants**

Children with immune thrombocytopenia (ITP) attending NHS outpatient appointments in relation to their condition with their parents/carers were eligible for the study. Participants were approached if they had persistent ITP (>3 months duration), chronic ITP (>12 months duration), or recently recovered ITP (platelet count normal but identified by clinician as having ITP, with abnormal blood count in the previous 6 months). Children had to be at least 4 years old to be included in the study (using parent report) and were eligible to complete self-report measures from the age of five.

Participants were excluded if they had developed ITP as a result of a bone marrow transplant as it was felt that the issues presenting in this group would be significantly different from the rest of the cohort. For the same reason, children were also excluded if they had another medical condition or disability that was poorly controlled or active at the time of the study. Families with a poor command of English were excluded if an interpreter was not already available through the clinic, and/or if language translations were not available in the research measures. One family was excluded due to language ability; two families were excluded due to the child having co-morbid condition. In total, 46 families were invited to participate. Figure 3 outlines the flow of participants through the study.

Figure 3: Participant flow diagram



In total, at least one questionnaire was returned for 37 families. Thirty-five children ( $M = 10.1$  years,  $SD = 3.47$ ) and 35 parents ( $M = 43.2$  years,  $SD = 5.71$ ) participated. This indicates that in the majority of cases (89%), both children and parents from the same family chose to participate. Table 1 summarises the demographics for children and parents that participated. There was a significant range in length of diagnosis of ITP between 3 months and 86 months (8 years), with an average diagnosis length of 32 months. Six children (16% of the sample) were classified with persistent ITP, whilst 31 children (84%) had chronic ITP.

Table 1: Demographics for participants

Demographics		Participant	
		Child N=35	Parent N=35
Gender	Male	20 (54.1%)	10 (27%)
	Female	17 (45.9 %)	22 (59.5%)
	Missing		3 (8.1%)
Mean age		10.1 years	43.23 years
(range, <i>SD</i> )		(5-16 years, 3.47)	(31-58 years, 5.71)
Ethnicity	White British	19(54.3%)	15 (40.5%)
	White other	4 (11.4%)	5 (13.5%)
	Black African	1(2.9%)	3 (8.1%)
	Indian	3(8.6%)	2 (5.4%)
	Pakistani	2(5.7%)	2 (5.4%)
	Other Asian		2 (5.4%)
	Background	1(2.9%)	
	Black African and		-
	White	2(5.7%)	
	Asian and White	1(2.9%)	-
	Other Dual		-
	Heritage	1(2.9%)	
	Other Ethnic		2 (5.4%)
	Group	1(2.9%)	
	Data missing		-



## **2.2 Sample size calculation**

Sample size calculations were based on the main research questions. The largest of these calculated samples was 51 and only this calculation is reported. This concerned levels of fatigue in child patients with ITP. No study has been conducted for fatigue in children with ITP. However, a study comparing fatigue scores for those with sickle cell (another blood disorder) with a sample from the general population found large effects sizes (0.96) for parent reports. Using this in a calculation, 15 participants would be required to detect this difference, using a one-tailed t-test of the difference between group means, at a power of 80%, and a significance level of 5%. However, sickle cell is more severe in symptom presentation and therefore a more conservative estimate of effect size was adopted. Using a moderate effect size of 0.5, 51 participants would be required under the same test parameters.

In order to increase recruitment, a researcher aimed to be at all clinical appointments. Clinicians were aware of the study in advance of the start of recruitment and attempts were made to schedule appointments, as appropriate, within the data collection period. Follow up telephone calls were made when questionnaires were not returned. A third clinical site was considered but the advantages of increasing sample size were balanced by the effect on the heterogeneity of the sample and the changes required to the agreed procedure.

## **2.3 Measures**

Measures were chosen which were appropriate to the paediatric population being studied, that were relatively brief to self-complete and administer, that had the potential to capture both parents' and children's perspectives, and that covered the age range of interest. Certain measures were favoured for their availability of language translations and standardised norms. The specific rationale for the measures used is given below.

### **2.3.1 Total Difficulties (Strengths and Difficulties Questionnaire)**

The Total Difficulties score was taken from four factors of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) (Appendices 1 & 2) and used for a measure of emotional and behavioural functioning. This combines the scores from the subscales of emotional symptoms, conduct problems, hyperactivity/attention, and peer relationship problems. The total score can range from 0-40. Use of this score allows comparison with studies where scores have not been separated into individual subscales. Two subscales were also used separately in analysis (see below), with totalled scores possible between 0-10 for each subscale.

The SDQ allowed for assessment across the whole age range of our desired sample using parent report and allowed self-report from young people aged 11 years and over. This Total Difficulties score has more robust psychometric properties than individual subscales, including better test-retest reliabilities (0.72 for parent report, 0.62 for child self-report) and high

internal consistency (Cronbach's  $\alpha = 0.82$  for parent report,  $\alpha = 0.80$  for child self-report) (Goodman, 2001), with good discrimination using this score between those with a diagnostic disorder and those without (Essau et al., 2012).

### **2.3.2 Emotional Symptoms (SDQ)**

Emotional functioning was assessed using the Emotional Symptoms subscale of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997). This subscale combines items about worry, fear and nervousness, low mood and somatic symptoms. The subscale has acceptable internal consistency in parent and self-reports (alpha values: parent = .67, child = .66) (Goodman, 2001; Stone, Otten, Engels, Vermulst & Janssens, 2010) and correlates with other measures of emotional functioning (Essau et al., 2012, Goodman, 2001; Stone et al., 2010).

### **2.3.3 Conduct Problems (SDQ)**

The Conduct Problems subscale of the Strengths and Difficulties Questionnaire (Goodman, 1997) was used to measure behavioural difficulties. This subscale has acceptable internal consistency (parent  $\alpha = .63$ , child  $\alpha = .60$ ), stability over time and high specificity for identifying individuals without a relevant mental health diagnosis (Goodman, 2001).

#### **2.3.4 Pediatric Quality of Life Inventory™ (PedsQL™): Multidimensional Scale for Fatigue**

The 18-item Pediatric Quality of Life Inventory™ (PedsQL™): Multidimensional Scale for Fatigue (Varni, Burwinkle, Katz, Meeske, Dickinson, 2002) was used to measure fatigue (Appendices 3-5). This has good internal consistency (alpha,  $\alpha = .95$  child report,  $.95$  parent report). It covered the full age range of the study population (for parent report), and allowed children over five years old to self report (5-7 year olds were assisted by interviewer). It has been developed specifically for assessing the quality of life of children with health conditions. A higher score indicates lower problems with fatigue.

#### **2.3.5 Behaviour Rating Inventory of Executive Functioning (BRIEF)**

Executive function difficulties were measured using parent informant report on the 86-item Behaviour Rating Inventory of Executive Functioning (BRIEF) (Gioia, Isquith, Guy & Kenworthy, 2000a) (Appendix 6). This was preferred to cognitive testing due to the time that would have been required to complete cognitive tests and it was not felt this was appropriate for the study. This measure has good reliability, with high test-retest reliability ( $.82$  for parents) and internal consistency ( $\alpha = .98$ ) (Gioia, Isquith, Guy & Kenworthy, 2000b).

### **2.3.6 Kid's ITP Tools (KIT)**

The Kid's ITP Tools (KIT) (Klaassen et al., 2007) (Appendices 7 & 8), an ITP-specific quality of life measure for children, was administered. This questionnaire includes items about emotional and physiological symptoms, which allowed comparisons with other measures in this study, as well as specific concerns and issues around ITP such as bloods tests, bruising and potential worries around platelet count. Two versions, assessing quality of life from the child's perspective and child's quality of life from the parents' perspective were used. This has been shown to have acceptable test-retest reliability (Intra-class correlation > 0.70) (Klaassen et al., 2007).

### **2.3.7 Visual Analogue Appraisal Scales (Appendices 9-11)**

Visual analogue scales (VAS) were constructed to investigate both parents' and children's cognitive appraisals of ITP. These were constructed using adapted items primarily from the Child Attitude Towards Illness Scale (CATIS, Austin & Heberty, 1993), the Uncertainty in Illness Scale (Mullins & Hartman, 1995), and the Parent Experience of Child Illness Scale (PECI, Bonner et al., 2006). These measures were felt to be inappropriate for this study due to their length and the specific wording of certain items. Construction of the VAS measure was done in consultation with three project supervisors, all Clinical Psychologists, and a Haematology Consultant.

Two VAS forms were created for children- one for children aged 5-6 and the other for children aged 7-16 years. For the older children (7 years and older) and parents, the visual analogue scales covered the child and parent's subjective severity rating of the condition, its impact and their perceived coping ability. Wording was kept consistent across parent and child scales and all items were on a five point (0-5) Likert scale. There was also a space available for qualitative report of the aspect of ITP that 'bothers you the most'. This terminology was selected as it is also used in the Kids ITP Tools (Klaassen et al., 2007). The VASs were trialled with two 11 year olds from a non-clinical population. They confirmed that the format made sense and no further amendments were made. Younger children (5-6 years) completed a simplified version which included how bad they would rate their illness using a 5-point Likert scale with faces and the aspect of ITP that bothers them the most. This format was chosen because it is the same as the version of the PedsQL™ Multidimensional Fatigue Scale (Varni et al., 2002) for children aged 5-7 years.

### **2.3.8 Demographic and clinical factors**

Demographic information was obtained through the questionnaires or the clinical file and included gender, age and ethnicity for child and parent. Clinical factors were obtained from clinical records and included platelet count, bleeding severity, previous and current treatment course and side effects, length of diagnosis, co-morbid conditions, and the occurrence of a previous intracranial haemorrhage (Appendix 12 – clinical record form).

Platelet count and bleeding severity were rated from results from the most recent clinic attendance or the most recent blood results on file from the General Practitioner or other clinical site. Bleeding severity was judged using the standards from the Intentional Consensus Report on ITP management (Provan et al., 2010). This was used as it drew on several research developments of the topic, gave clear descriptors for clinicians and distinguished between minor and mild symptoms at the lower end of the symptom scale, applicable to the child population. Clinicians also gave a subjective rating of severity of illness based on their perception of the overall severity for the child, over the whole course of the illness, since diagnosis.

#### **2.4 Administration of questionnaires**

The order of the questionnaires was kept the same for all participants (within each age range). The order was: Strengths and Difficulties Questionnaire (Goodman, 1997), PedsQL™ Multidimensional Fatigue Scale (Varni et al., 2002), KIT (Klaassen et al., 2007), BRIEF (Gioia et al., 2000a) (parents only), visual analogue scale. The reason for this order was to prioritise the gathering of the SDQ data as our main outcome measure and also to take into account the demand and acceptability to the participants (not including the longest measure first or last).

The questionnaires given to each child and parent varied depending on age of the child. This is summarised in Table 2. Child questionnaires were estimated to take up to 15 minutes, although this was less for young

children who had fewer measures. This was verified with two 11 year olds from the general population prior to commencement of the study and was accurate to completion times observed in clinic.

Table 2: Summary of measures given to participants, dependent on child age

Age of Participant child (years)	Participant	Measures				
		Visual Analogue Scale	KIT	PedsQL™- Fatigue	SDQ	BRIEF
5-6	Child	✓		✓		
	Parent	✓		✓	✓	✓
7	Child	✓	✓	✓		
	Parent	✓	✓	✓	✓	✓
8-10	Child	✓	✓	✓		
	Parent	✓	✓	✓	✓	✓
11-16	Child	✓	✓	✓	✓	
	Parent	✓	✓	✓	✓	✓

*Note.* KIT= Kids ITP tools; PedsQL™-Fatigue= Pediatric Quality of Life Inventory™ Multidimensional Scale for Fatigue; SDQ= Strengths and Difficulties Questionnaire; BRIEF= Behaviour Rating Inventory of Executive Function



Parents were given five questionnaires, regardless of child age. The only difference between parent questionnaires was the versions of the fatigue scale, which were different dependent on the age of the child (four age-range versions). The questionnaires took approximately 15-20 minutes for parents to complete.

## **2.5 Procedure**

The research was conducted through paediatric haematology clinics in two NHS hospital sites in London. Potential participants were first made aware of the study through correspondence with their clinician or during their clinic appointment. Advertising materials (Appendix 13) were also displayed at one of the clinic sites. A member of the research team then approached families who were attending their routine clinic appointments. The researcher explained the project and obtained informed consent.

Information sheets were given to children and parents (Appendices 14-16). The purpose and procedure of the study was outlined clearly. For child participants, verbal or written assent (Appendix 17) was obtained from those 5-15 years old, with written parental consent. Young people aged 16 years and over and parents gave written consent for themselves (Appendices 18 and 19). Parents were allowed to participate if their child did not want to complete questionnaires; children were allowed to participate (with parental consent) if their parents declined to be participants themselves. There were two instances of children participating where parents did not return

questionnaires. There was one family where the parent completed questionnaires and the child declined, and an additional one family where only the parent participated due to age of the child.

Parents and children were then given questionnaire measures to complete by the Chief Investigator, who was available in person to answer any questions. Where participants did not have a good command of English, translated measures were used if available or an interpreter was used if present already through the clinic appointment. An interpreter was used with three families. The Arabic version of the SDQ was offered to one parent, but instead they expressed a preference for translation of the English version through an interpreter available. The SDQ French version was given to one parent (child of the same family used the English version) but this parent was happy and able to use the English versions of the other measures.

Families often had to wait for blood tests and results, which allowed time for the completion of questionnaires in clinic. If completing measures on site, families had the option to complete in a private clinic room with the Chief Investigator present or in the waiting area. Children were not separated from their parents. A prompt was given to parents and children to not discuss their responses until completion, where this was observed to be occurring. Families also had the option of taking the measures away and returning them by post. On four occasions, due to the timing of clinic appointments, families were contacted by phone about the research after initial introduction

from the clinical team and questionnaires were sent out by post. Participants were contacted three weeks after receiving questionnaires to prompt their completion and answer any outstanding questions regarding the study, as explained in the information sheet for the study.

Demographic information about the child and adult participant was obtained through a self-report questionnaire completed by parents (Appendix 20) and/or through the clinical notes, with consent. Clinical information on disease related factors was obtained from patient records via the clinical team with explicit consent from relevant party (young person or parent). Researchers outside of the clinical team did not have direct access to clinical records. Clinical information was provided on separate forms and linked to questionnaire responses by means of a unique indentifying code. Data collected was stored in line with University, NHS (local and national) and professional guidelines and policies.

Parents and young people were asked if they would like to be contacted regarding the results. Where this offer was accepted, families provided contact details, typically in the form of an email address. Thirty-three families requested this summary.

## **2.6 Ethical Considerations and Approval**

The study was approved by Royal Holloway Research Ethics Committee, NHS Research Ethics Committee, an additional research governance committee associated with the lead hospital site and other local site approvals including from the two NHS Trust Research and Development Departments (Appendices 21-26).

The procedure was assessed to not be too demanding on participants, both in terms of time and nature of the questions asked. Families appeared happy to complete questionnaire and no distress was observed through completion. Participants were given the full rationale for the study, with no deception employed. Information sheets were constructed for different age ranges of children to facilitate understanding of the project.

## **2.7 Service User Involvement**

Service user involvement results in better quality research that is meaningful and of interest to the population and wider society the research serves (INVOLVE, 2012). Furthermore, involving service users in research fosters a sense of empowerment and respect, and this may be particularly significant for children, who may feel their opinions are not always taken in to consideration. Best practice guidance (Department of Health, 2005) states that service users should be involved at each stage of research where possible and funding and ethics boards now require careful consideration of how and when service users may be involved.

For this study, the concepts and themes to be investigated were highlighted at a one day joint patient convention and professional conference run by the ITP Support Association in April 2014, prior to finalising the research procedure. This was to assess whether the broad research themes were of interest and relevance to people who had experience of ITP. This was attended by the Chief Investigator (doctoral student) and a Haematology Consultant from one of the hospital sites. Attendees were not aware of our attendance prior to the event but discussion took place on an ad hoc basis, with agreement from the organisers and in keeping with the format and expectations of the event. Discussions were had in small groups, one group which was specifically for children with ITP and/or their parents. Subsequent discussions took place on the day with individuals, as they volunteered themselves. The idea behind the research was well received. In particular, attendees with ITP (and their family members) seemed interested in the area of fatigue and this was reported as a major problem for adults and children with ITP.

Members of the public (without ITP) and a child with ITP and their parent provided feedback on materials used in the study. Amendments included minor changes to wording and structure to make documents more accessible and clarify what was being asked of participants. One young person approached in clinic for participation expressed a particular interest in the study and was subsequently contacted to help construct an accessible summary of the results (Appendix 27).

## **2.8 Analysis plan**

### **2.8.1 Preparation of data.**

Scores on all measures were examined for normality using calculated figures for skew and kurtosis, and by visual inspection of the data in graphical format. The data was also inspected for outliers and, where relevant, calculations were made to determine the extent of discrepancy of the outlier from the mean. Negativity and inconsistency scores were examined to check validity of responses on the BRIEF measure (Gioia et al., 2000a); a score of 5 or above for negativity was considered high. This could indicate responder bias or high executive problems for the target child. On the inconsistency scale for the same measure, a score of 6 or less was considered within acceptable bounds.

For the Strengths and Difficulties Questionnaire (Goodman, 1997), each sub-scale has five items contributing to it. Items were scored from 0 (not at all true), 1 (somewhat true), or 2 (certainly true). Each subscale score can range from 0 to 10. Pro-rata values were used for missing values where at least three scores were present (i.e. no more than two missing values) for a particular scale. For the BRIEF measure, in accordance with the protocol suggested in the manual (Gioia et al., 2000a), for subscales with one or two missing values, missing values were replaced with a score of 1. Where more than 2 scores were missing, T scores were not calculated for the subscale or any derived scores. For the PedsQL™-Multidimensional Fatigue Scale (Varni et al., 2002), scores were not computed if more than 50% of the items

were missing from a particular scale. For the KIT summary score to be calculated, no more than 6 items could be omitted.

### **2.8.2 Categorisation of scores.**

SDQ scores were considered in a four band categorisation: 'Close to average', 'slightly raised', 'high' and 'very high' (Goodman, 2013). 'Abnormal scores' are described as falling within the latter three categories. Approximately 80% of the child population have scores 'close to average', whilst only 5% of children would have scores in the 'very high' range. BRIEF values were converted in to T scores, which are linear transformations of raw scores, allowing comparison with a standardised sample. Scores of 65 or higher (+1.5 *SD* from the mean) were considered to indicate problems with executive function. In line, with scoring instructions, low fatigue scores represented worse fatigue.

### **2.8.3 Analyses.**

Data was analysed using Statistical Software for Social Scientists (SPSS) version 21. Unless otherwise stated, alpha value for significance was considered as  $p < 0.05$ . T-tests were carried out to explore gender differences and answer the questions concerning the difference of data scores from published comparable samples and normative values. Where study scores were compared to published norms or data from another sample, GraphPad software (Motulsky, 2015) was used to test this difference. Correlation coefficients were calculated to test the association between variables. This was used to address the research question

regarding clinical condition factors (including platelet count) and adjustment variables, and the relationships between fatigue, executive functioning, emotional-behavioural functioning, appraisal and quality of life. Associations within each measure (i.e., between subscales) are not discussed. Qualitative comments from the KIT and VAS were reviewed and themes extracted.

### **3. Results**

After description of the normality of the data and reliability of the Visual Analogue Appraisal Scale, results are presented in four main parts. The first discusses demographic and clinical information and explores the relationship of age and gender with the outcome variables. For fatigue, groups were also examined on the basis of active treatment. The second part of the results examines the main research questions concerning difference in outcomes of children with ITP compared with healthy children and children with sickle cell disease (SCD). The third part examines the relationship between variables, firstly testing the association between clinical information and adjustment outcomes and then the inter-relationships between adjustment outcome variables. Finally, appraisal and qualitative comments are explored. Where measures were completed by both parent and child, these are discussed in turn.



### **3.1 Normality**

Inspection of all measures, except the platelet count, showed the scores to be normally distributed, with measures for skew and kurtosis within normal bounds. Applying a square root transformation of the platelet count returned values to acceptable bounds. Outliers were identified within some responses but these were within three standard deviations of the means for these scales.

### **3.2 Visual Analogue Appraisal Scale - Reliability and Validity**

The Visual Analogue Appraisal Scale for parents (five items) and the children's scale (1 or 3 items, depending on age) were tested for internal consistency using Cronbach's alpha. The parent scale was shown to have good internal consistency ( $\alpha = .81$ ). Analysis showed that removing any of the items, except parent's rating of child's coping would decrease this alpha value. Removing the 'child coping' item would increase reliability to .83. This item also correlated poorly with other items, which could suggest it should be removed. The child scale showed a poor level of reliability ( $\alpha = .65$ ). Analyses indicated that removing the item of child's rating of their own coping would increase the scale's reliability to .87, a good level of reliability. This demonstrates that items from each scale are related and seem to be measuring the same overall construct. These results confirmed that scores from this scale could be used the main analyses.

Parents' rating of the amount their child's life was affected as rated on the Visual Analogue Appraisal Scale (VAS) was significantly associated with parents' quality of life rating for child ( $r(30) = -.47, p = .006$ ), which supports the construct validity of this item of the VAS. There was a similar correlation on the child rating of their quality of life with their rating on the VAS of the extent their life affected ( $r(22) = -.44, p = .03$ ).

### **3.3 Demographics**

Information for the children with ITP is presented in Table 3. The sample was an approximately equal split of girls and boys (17 girls, 20 boys). The average age was 9.84 years ( $SD = 3.61$ ). Most children (84%) had chronic ITP (of duration over 12 months), with the average length of diagnosis as 31.9 months (range = 3-96 months). The average platelet count was 84.2 ( $\times 10^3$  platelets / micro litre) ( $SD = 80.54$ , Range = 1-286). Seven children had counts over 150 ( $\times 10^3$  platelets / micro litre). As discussed, it was confirmed that these children had abnormal counts within the last six months. Bleeding severity as rated by clinicians was generally low, with only one patient rated as moderate bleeding severity; the remaining children had minor-mild bleeding or no bleeding.

Most children (78.4%) were not receiving active treatment. Of those on treatment, no side effects were observed or reported. Thirteen children (35.1%) had never had previous active treatment. Only one child had previously had an intra-cranial bleed. Eleven children (30% of sample) had

other conditions. Some children had more than one co-morbid condition. These were all judged clinically to be well-managed and stable. Three children were also identified as having conditions previously, including previous vitamin D and iron deficiency, recurrent tonsillitis, and CMV infection.

Table 3: Demographics and clinical data for the sample of children with ITP

Characteristic	Number of children (%) N= 34
ITP type	
Persistent	6 (16)
Chronic	31 (84)
Current treatment (%)	
No active treatment	29 (78.4)
Tranexamic acid	3 (8.1)
IVIg	1 (2.7)
Rituximab	1 (2.7)
Combination	1 (2.7)
Other	2 (5.4)
Other conditions <sup>a</sup>	
Asthma	2 (5.4)
Diabetes	1 (2.7)
Eczema/ Dermatitis	2 (5.4)
Evan's syndrome	2 (5.4)
Klinefelters and congenital talipes equinovarus	1 (2.7)
Mild IgA and IgM deficiency	1 (2.7)
Mild undefined joint pain	1 (2.7)
Molluscum	1 (2.7)
Recurrent tonsillitis	1 (2.7)
Rhinitis	1 (2.7)
Undiagnosed gastrointestinal problems	1 (2.7)
Previous ICH bleed	1 (2.7)

<sup>a</sup> Some children had a combination of more than one co-morbid condition

Demographic information of age and gender was examined across the various adjustment measures in order to determine their significance in the analyses relating to the main research questions.

Mean scores for each gender on emotional and behavioural difficulties (Emotional Symptoms, Conduct and Total Difficulties) from the Strengths and Difficulties Questionnaire are displayed in Table 4.

Table 4: Gender comparisons for total subscale scores on the Strength and Difficulties Questionnaire (SDQ), averaged across participants

SDQ Subscale	Boys		Girls		<i>t</i>	<i>df</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>		
Child Self report						
	<i>N</i> = 9		<i>N</i> =8			
Emotional Symptoms	2.00	1.50	4.0	1.77	-2.52	15
Conduct Problems	2.22	1.39	1.75	1.28	0.72	15
Total Difficulties Score	9.0	5.5	8.88	4.42	0.05	15
Parent proxy-report						
	<i>N</i> =19		<i>N</i> =16			
Emotional Symptoms	2.74	2.16	3.63	1.78	-1.31	33
Conduct Problems	2.26	1.82	1.81	1.33	0.82	33
Total Difficulties Score	10.84	6.78	9.75	4.85	0.54	33

*Note.* SDQ subscale scores can range from 0-10; SDQ Total Difficulties score can range from 0-40.

\*Test significant at .05 level (2-tailed). \*\*Test significant at .01 level (2-tailed).

For parent ratings, no subscales showed significant differences for gender. For child ratings, there were no significant differences based on gender for Conduct Problems or Total Difficulties. The Emotional Symptoms subscale showed a significant difference for the two genders, with girls reporting significantly more problems.

Age was negatively correlated with the Emotional Symptoms subscale of the SDQ for parent ratings ( $r(33) = -.375, p = .027$ ), indicating older children were reported to have fewer emotional problems. There were no correlations for any of the SDQ scales with age for the children's ratings.

There were no significant differences between boys and girls on fatigue measures, for both parent and child ratings (Table 5). Individual Pearson's correlations were carried out between age and fatigue scores. Due to multiple comparisons (eight comparisons) across subscales, a  $p$  value of 0.0063 was selected. The only scale that approached significance was sleep fatigue as rated by children ( $r(32) = -.45, p = .007$ ).

To investigate whether findings would be analogous to those found with adults with ITP and fatigue (Newton et al., 2011), analysis was carried out on the sample to determine if there were any differences in fatigue between those on treatment and those not on active treatment. Those on treatment (seven children) experienced significantly worse total fatigue than those on

observation only ( $t(32) = 2.98, p = .005$ ), as rated by parents but there were no differences between child ratings ( $t(32) = 1.78, p = .084$ ).

Table 5: Mean subscale scores of fatigue for boys and girls

Subscale	Boys		Girls		<i>t</i>	<i>df</i>
	<i>M</i>	( <i>SD</i> )	<i>M</i>	( <i>SD</i> )		
Child self-report						
	<i>N</i> =18		<i>N</i> =16			
Total fatigue	71.67	(14.71)	68.54	(17.23)	0.57	32
General fatigue <sup>a</sup>	79.17	(12.78)	67.22	(22.38)	1.92	31
Sleep fatigue	65.19	(20.73)	69.48	(17.59)	-0.65	32
Mental fatigue	70.60	(23.50)	69.53	(21.18)	0.14	32
Parent proxy-report						
	<i>N</i> =19		<i>N</i> =15			
Total fatigue	66.76	(19.90)	68.61	(14.52)	-0.30	32
General fatigue	67.02	(19.57)	67.22	(18.69)	-0.03	32
Sleep fatigue	68.20	(19.31)	68.06	(15.80)	0.02	32
Mental fatigue	65.35	(28.50)	70.56	(18.80)	-.64	32

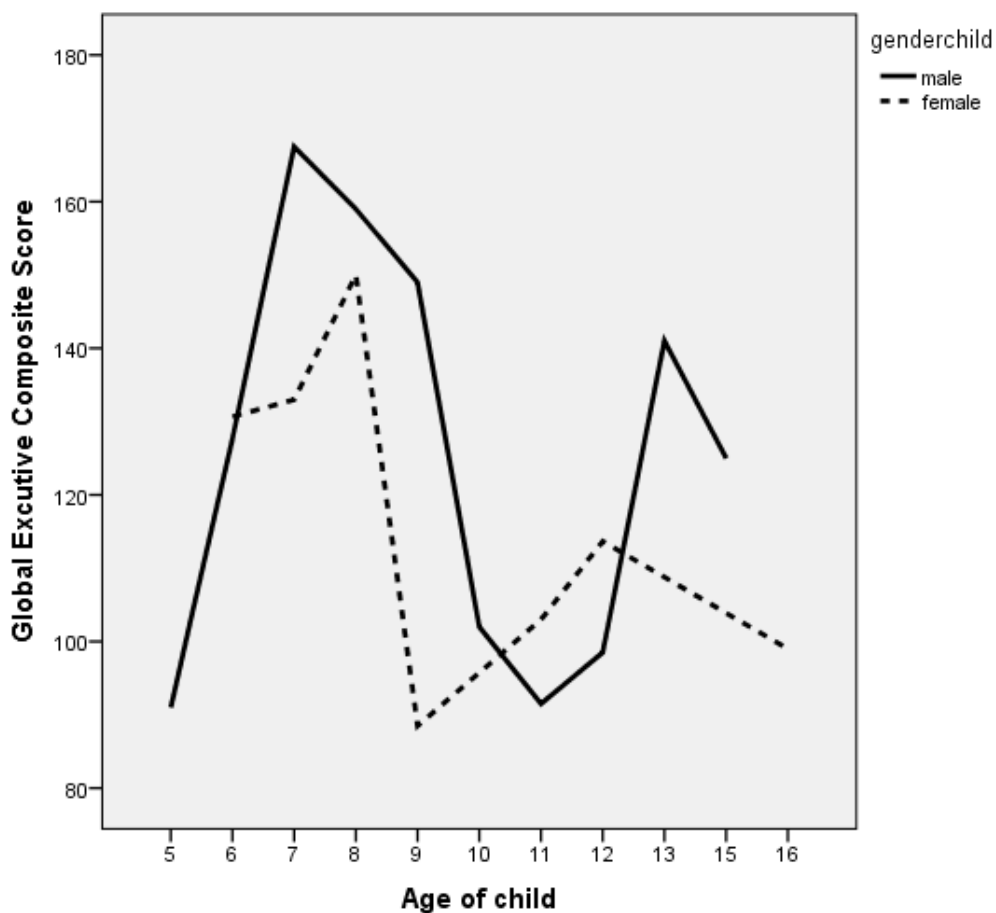
*Note.* A higher score indicates lower problems with fatigue

<sup>a</sup> *n* = 15 girls

Visual examination of the executive functioning data (from the BRIEF) showed different patterns of scores for girls and boys (Figure 4). Boys showed heightened problems around the age of 7 years and around 13

years. Girls showed high problems around age 8 and some elevation at a later age (age 12) but not to the extent seen in boys. These patterns should be considered with caution as often only 1-3 data points contributed to each age for each gender. However, the patterns parallel those reported by the authors of the scale, who commented on an interaction pattern between age and gender where boys experienced greater problems with executive function that decreased with age (Gioia et al., 2000b). Considering this information, and to allow comparison with published comparison scores/norms, T scores (linearly transformed scores relative to a standardised sample) were calculated and used in statistical analyses.

Figure 4: Global executive functioning by age and gender





Analysis of the effect of gender on quality of life scores (Table 6), indicated no significant difference of gender for parental reports ( $t(31) = 0.266, p = .792$ ) or child reports ( $t(22) = 1.62, p = .119$ ). There was no correlation of age with quality of life for parent ( $r(31) = 0.253, p = .155$ ) or child ratings ( $r(22) = 0.098, p = .648$ )

Table 6: Mean (SD) quality of life scores from Kids ITP Tools (KIT)

Parent proxy KIT score		Child self-report KIT score	
Male N=19	Female N=14	Male N=12	Female N=12
78.77 (14.99)	77.40 (14.19)	84.03 (12.55)	74.73 (15.43)

In summary, only limited associations were found between demographics of age and gender with study variables. These included a gender difference on Emotional Symptoms and a trend association with age and fatigue. As the current sample comprised approximately equal numbers of girls and boys it was still appropriate to carry out the planned analyses as a single combined group. Also, dividing the group would have resulted in smaller samples and may have increased the chance of Type II error in the study. The associations of age and gender for BRIEF scores were controlled through conversion of raw scores to T scores.

### **3.4 Profile of adjustment in ITP: Comparison with Other Samples**

#### **3.4.1 Total difficulties (emotional and behavioural functioning).**

For parental report, most children were rated as not having difficulties with emotional and behavioural functioning. However, 14.4 % of children (5 children) were rated in the high-very high range on total SDQ score, 4 of these (11.5% of valid sample) were rated in very high range. By comparison, only 5% of children in the normal population have scores in this very high range (Goodman & Goodman, 2011). For child reports, the total SDQ score for two children fell within an abnormal range, with one classed as slightly raised, and the other as very high.

In order to establish whether emotional and behavioural difficulties were significantly higher in this sample of children with ITP compared with the normal population in line with research questions, t-tests were carried out. Normative values published in a study by the Office of National Statistics (Meltzer, Gatward, Goodman, & Ford, 2000) were used for comparison (Table 7). In order to use a comparative sample, only reports from parents relating to 5-15 year olds were used for this analysis (4 year olds and 16 years olds were excluded). Normality checks were re-run on this sample. All scores were within acceptable bounds, with no display of skew. Total Difficulties score rated by parents was significantly different from normative values ( $t(10328) = 2.4102, p = .02$ ). This was a small to moderate effect size. Child self-report scores of Total Difficulties were not significantly different from normative values ( $t(4243) = 1.0756, p = .28$ ). These results indicate

that children with ITP did have higher rates of emotional and behavioural difficulties compared to healthy children based on parental report of difficulties, but not on child ratings of difficulties. In order to examine this result in more detail, Emotional Symptoms and Conduct Problems subscales were also compared to the normative values.

Table 7: Comparisons of parent and child mean scores on Strengths and Difficulties subscales with normative values

Subscales	ITP sample		Normative comparison		<i>t</i>	<i>df</i>	<i>d</i>
	<i>M</i>	<i>S.D</i>	<i>M</i>	<i>S.D</i>			
Child self-report							
	N=14		N=4228				
Emotional Symptoms	2.43	1.45	2.8	2.1	0.66	4240	0.18
Conduct Problems	2.00	1.24	2.2	1.7	0.44	4240	0.12
Total Difficulties Score	8.5	4.62	10.3	5.2	1.29	4240	0.35
Parent proxy report							
	N=32		N=10298				
Emotional Symptoms	3.25	1.97	1.9	2.0	3.81**	10328	0.68
Conduct Problems	2.19	1.61	1.6	1.7	1.95	10328	0.35
Total Difficulties Score	10.88	5.78	8.4	5.8	2.41*	10328	0.43

*Note.* *d*=effect size (Cohen's *d*)

\*Test significant at the 0.05 level (2-tailed). \*\*Test significant at the 0.01 level (2-tailed).

### **3.4.2 Conduct problems.**

Six children (17.2%) were rated by their parents to have conduct problems that were in the high-very high range, although only one of these was in the very high range. Three children rated themselves as having problems with conduct that could be considered 'slightly raised'. No children reported problems that reached the high level of problems. As seen in Table 7, the difference on the SDQ subscale for Conduct was close to significant for parent ratings. This was a small to medium effect size and the finding of no statistical significance should be considered with the small sample size. However, these results indicate that behavioural problems were not higher for this sample.

### **3.4.3 Emotional functioning.**

Just over half the children (51.4%) were rated by parents as having scores on the Emotional Symptoms subscale within the 'close to average' range, 22.9% scored in the 'slightly raised' range, 25.8% (a quarter of valid sample) in the 'high' or 'very high' range (only one person scored as very high). Parental reports of emotional difficulties were significantly higher for the ITP group than normative values ( $t(10328) = 3.81, p = .001$ ) (Table 7). This was a medium to large effect. Two children rated their emotional symptoms as above normal, with one categorised as high, the other as very high. Children's ratings of their own emotional symptoms, as reported on the SDQ was not significantly different from the normative comparison group. Related to the first research question, this shows that Emotional Symptoms were

worse for a larger proportion of children with ITP, compared with a normal population but based on parents' ratings only.

#### **3.4.4 Fatigue.**

In order to examine the first research question in relation to fatigue, fatigue scores for this sample were compared from those for healthy controls taken from data published by Panepinto and colleagues (Panepinto et al., 2014). Table 8 shows the means for the both samples. As discussed, higher fatigue scores indicate lower problems. There were significant differences on both total and all subscale scores for fatigue, between ITP participants and healthy controls, for both parent and child ratings. The effects sizes for these ranged from small (for sleep fatigue as rated by children) to large (for general, sleep and total fatigue ratings from parents). In answer to the first research question, this indicates that within the sample, children with ITP did have greater levels of problems with fatigue compared to healthy children. Effects were larger depending on person reporting (parent or child), with parent reports generally showing larger effects. Two parents additionally commented elsewhere in the questionnaire packs that tiredness or energy levels were a particular issue for their child/the issue that bothered them as parents the most.

Table 8: Comparison of mean fatigue scores in children with ITP and healthy children

Measure	ITP sample		Healthy sample		<i>t</i>	<i>df</i>	<i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Child Self report							
	<i>N</i> =34		<i>N</i> =209				
Total fatigue	70.20	15.78	81.8	12.5	4.83**	241	0.62
General fatigue <sup>a</sup>	73.74	18.50	86.1	13.6	4.60**	240	0.60
Sleep fatigue	67.21	19.15	76.8	16.3	3.10**	241	0.40
Mental fatigue	70.10	22.11	82.4	16.5	3.83**	241	0.50
Parent proxy-report							
	<i>N</i> =34		<i>N</i> =209				
Total fatigue	67.58	17.50	88.2	11.1	9.42**	291	1.10
General fatigue	67.11	18.90	88.8	12.3	9.00**	291	1.10
Sleep fatigue	68.14	17.58	87.6	13.5	7.61**	291	0.90
Mental fatigue	67.65	24.49	88.2	16.0	6.56**	291	0.77

*Note.* *d* = effect size (Cohen's *d*). A higher score indicates lower problems with fatigue

<sup>a</sup> *n* = 33.

\*Test significant at the 0.05 level (2-tailed). \*\*Test significant at the 0.01 level (2-tailed).

As an exploratory analysis, scores for fatigue from this study were compared with a sample of children with sickle cell disease from a published study (Panepinto et al, 2014). There were no significant differences between parent rated scores on the total fatigue score or any fatigue subscale. However, there were significant differences between child ratings of fatigue between those with ITP and those with sickle cell, on total and all subscale measures, with children with ITP rating themselves as less fatigued. (total fatigue,  $t(272) = 2.57, p = .01$ , general fatigue,  $t(271) = 2.02, p = .04$ , sleep fatigue,  $t(272) = 2.15, p = .03$ , mental/cognitive fatigue,  $t(272) = 2.33, p = .02$ ). In relation to the first research question, concerning fatigue levels in children with ITP, it seems that although fatigue levels were higher than healthy children, they may be the same or better compared with children with sickle cell disease.

#### **3.4.5 Executive functioning.**

BRIEF scores were examined on two validity checks available as part of the measure. One person scored 5 on the Negativity check. This could indicate the responder parent is negatively biased in their responding style or reflect a real and substantial deficit for the child being commented on. Examination of inconsistency scores indicated that all respondents were classified as within acceptable bounds of consistency.

Five children (16.5%) had T scores of 65 or over on the Behaviour Regulation Index. Six children (19.9%) had T scores of 65 or above for

Meta-cognition Index. Six children (19.9%) had T scores of 65 or above for Global Executive Composite. In order answer the first research question, overall executive functioning scores (Global Executive Composite) were compared with normative values using t-tests (Table 9). In comparison, there were significant differences on Global Executive Composite Score, indicating possible higher rates of difficulties in executive functioning for this sample of children with ITP. Removing the case with elevated 'Negativity' score from analysis, this difference remained statistically significant, ( $t(1446) = 2.11, p = .035$ ). In answer to the first research question, there appeared greater executive functioning problems for children with ITP. However, this was a small to moderate effect, and reflects that a large proportion of the sample (80%, 25 children) had scores within a normal range. Post-hoc examination of other scores revealed that executive functioning measured on Emotional Control and Initiation subscales, and the Behaviour Regulation Index were also significantly worse for this group ( $t(1448) = 4.86, p < 0.001$ ;  $t(1448) = 2.21, p = 0.03$ ;  $t(1447) = 3.06, p = 0.002$ , respectively). There was a small to moderate effect size for presence of ITP on Initiation but moderate and large effect sizes for Behaviour Regulation and Emotional Control, respectively.



Table 9: Comparisons of mean executive functioning (BRIEF) scores with normative *t*-test values

Scale	ITP sample		Healthy sample		<i>t</i>	<i>df</i>	<i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
	N= 31		N=1419				
Inhibit	52.07 <sup>a</sup>	11.55	50	10	1.12	1447	0.21
Shift	53.06	10.64	50	10	1.69	1448	0.31
Emotional Control	58.87	12.15	50	10	4.86**	1448	0.88
Behaviour Regulation	55.67 <sup>a</sup>	11.67	50	10	3.06**	1447	0.57
Initiate	54.03	11.67	50	10	2.21*	1448	0.40
Working Memory	53.19	10.17	50	10	1.76	1448	0.32
Plan/Organise	51.73 <sup>a</sup>	11.69	50	10	0.94	1447	0.17
Organisation of materials	53.10	9.33	50	10	1.71	1448	0.31
Monitor	51.97	10.64	50	10	1.08	1448	0.20
Meta-cognition Index	52.70 <sup>a</sup>	11.04	50	10	1.46	1447	0.27
Global Executive Composite	54.37 <sup>a</sup>	11.63	50	10	2.36*	1447	0.44

*Note.* BRIEF= Behaviour Rating of Executive Functioning; *d* = effect size (Cohen's *d*)

<sup>a</sup> *n* = 30

\*Test significant at the 0.05 level (2-tailed). \*\*Test significant at the 0.01 level (2-tailed).

Exploratory *t*-test analysis was carried out to examine the profile of executive function abilities compared with a sample of children with sickle cell disease (Hensler et al., 2014). To make the best comparison with the age range of the sample of children with sickle cell disease, only scores for children aged over 8 years were selected from the current sample. No significant differences were found on Indices of Behavioural Regulation, Meta-Cognition or Global Executive Composite for this sample compared to a comparative sample of children with sickle cell (Table 10).

Table 10: Comparisons of BRIEF scores between ITP participants and children with sickle cell disease (SCD)

	ITP sample <i>N</i> =21	SCD sample <i>N</i> =20		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>t</i>	<i>df</i>
Behaviour Regulation	53.0 (10.63)	54.3 (14.4)	0.33	39
Meta-cognition	50.48(10.67)	55.3 (13.3)	1.28	39
Global Executive Composite	51.67 (10.80)	55.2 (13.9)	0.91	39

### 3.5 Association between variables

Investigated variables were tested for associations using Pearson's bivariate correlations (Tables 11-13) to answer the second and third research questions.

### **3.5.1 Disease characteristics with adjustment outcome.**

Neither bleeding severity nor platelet count were significantly correlated with any of the fatigue scales for parents' or children's ratings (Table 11, Table 13). For parent ratings, neither bleeding severity nor platelet count score was significantly correlated with any of the Strengths and Difficulties Questionnaire scales.

For child ratings (Table 12), bleeding severity was highly negatively correlated with Conduct Problems ( $r(15) = -.64, p = .005$ ) and Total Difficulties ( $r(15) = -.64, p = .006$ ) on the Strengths and Difficulties Questionnaire. Higher bleeding severity was related to lower problems in emotional and behavioural functioning. As only one child had a bleeding severity of 3 (moderate), it may be that their low scores on the SDQ may have skewed these results. However, removing this case, the association between bleeding severity and these SDQ scores remained (Conduct,  $r(14) = -.56, p = .02$ ; Total Difficulties,  $r(14) = -.66, p = .006$ ).

### **3.5.2 Associations between adjustment outcome variables.**

Correlations were used to answer the third research question, regarding the associations between adjustment variables. Emotional functioning was negatively correlated to two (of the three) fatigue subscales (sleep fatigue and mental fatigue) and total fatigue (Table 11). As a higher fatigue score represents fewer problems with fatigue, this indicates that fewer problems with fatigue were associated with fewer problems on the Strengths and Difficulties Questionnaire. Total Difficulties score on SDQ was similarly

related to the same fatigue scales. Conduct significantly correlated to mental fatigue of the fatigue subscales. For child scores (Table 12), Emotional Symptoms were negatively correlated with general fatigue ( $r(14) = -.80, p < .001$ ), indicating higher levels of emotional problems were associated with high fatigue levels. Conduct problems were negatively correlated with mental fatigue scores ( $r(14) = -0.591, p = .016$ ), which parallels the responses from parents on these two variables. Related to the third research question there was some evidence that children's fatigue was related to their emotional and behavioural difficulties.

Associations between variables of executive functioning and other variables are shown in Table 14. Emotional symptoms were correlated with four BRIEF subscales (Shifting, Emotional Control, Working Memory and Planning), as well as all three composite scores. Conduct Problems and Total Difficulties correlated with seven of the BRIEF subscales. These two SDQ subscale scores and Total Difficulties score correlated with all composite scores (Behaviour Regulation, Meta-cognition and Global Executive), which partially answered the third research question, in that emotional and behavioural functioning was associated with executive functioning.

Fatigue subscales correlated with between four (for general fatigue) and seven subscales (for mental fatigue) of the BRIEF (Table 14). Related to the third research question, there was evidence that executive functioning difficulties correlated with fatigue. This indicates that higher levels of fatigue

were associated with greater difficulties in executive functioning. Additionally, the association between Emotional Problems (SDQ) and Global Executive Composite (BRIEF) ( $r(29) = .46, p = .009$ ), was no longer significant after controlling for fatigue ( $r(28) = 0.26, p = .16$ ), using partial correlation.

Table 11: Bi-variate correlations (Pearson's r) between variables for parents' response

Measure	1	2	3	4	5	6	7	8	9	10
1 Platelet count <sup>a</sup>	-									
2 Bleeding severity	-.41*	-								
3 SDQ- Emotion	.04	-.04	-							
4 SDQ- Conduct	.09	-.32	.22	-						
5 SDQ- Total Difficulties	.14	-.30	.64**	.78**	-					
6 Quality of life KIT score <sup>b</sup>	.12	-.41*	-.40*	-.33	-.39*	-				
7 Fatigue total	-.24	.07	-.44**	-.29	-.52**	.33	-			
8 General fatigue	-.18	-.05	-.23	-.14	-.27	.31	.87**	-		
9 Sleep fatigue	-.27	.027	-.39*	-.09	-.36*	.31	.87**	.76**	-	
10 Mental fatigue	-.19	.17	-.48**	-.45**	-.66**	.27	.85**	.56**	.55**	-

*Note.* *n* values varied between 30-35 depending missing data. SDQ = Strengths and Difficulties Questionnaire; KIT= Kids ITP Tools. Higher fatigue scores indicate lower problems with fatigue; negative correlations indicate lower fatigue problems correlate with low problems in other domains.

<sup>a</sup> Transformed score used for platelet count. <sup>b</sup> Proxy report

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).

Table 12: Bi-variate correlations (Pearson's r) between variables for children's responses, aged over 11 years

Measure	Platelet Count <sup>a</sup>	Bleeding Severity	Total KIT	General Fatigue	Sleep Fatigue	Mental Fatigue
SDQ - Emotion	.35	-.34	-.67**	-.59*	-.80**	-.39
SDQ - Conduct	.35	-.64**	-.10	-.56*	-.44	-.67**
SDQ - Total Problems	.43	-.64**	-0.36	-.77**	-.65**	-.84**

*Note.* *n* varied between 16 and 17, due to missing responses. SDQ = Strengths and Difficulties Questionnaire. KIT= Kids ITP Tools (quality of life measure). Higher fatigue scores indicate lower problems with fatigue; negative correlations indicate that lower SDQ problems correlate with lower fatigue problems.

<sup>a</sup> Transformed score used for platelet count.

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).

Table 13: Bi-variate correlations (Pearson's  $r$ ) between variables for children's responses, aged over 7 years

Measure	Platelet Count <sup>a</sup>	Bleeding severity	KIT score
KIT score	.04	.01	-
Fatigue total	-.14	.23	.69**
General fatigue	-.17	.21	.80**
Sleep fatigue	-0.19	.15	.36
Mental fatigue	-.01	.24	.54**

*Note.* KIT= Kids ITP Tools (Quality of life score).  $n$  varied between 33 and 34 for correlations, due to missing data. For correlations involving Quality of life (KIT) score,  $n = 24$ . Higher fatigue scores indicate lower problems with fatigue

<sup>a</sup> Transformed score used for platelet count.

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).



Table 14: Bi-variate correlations (Pearson's r) between executive functioning (BRIEF measures) and other study variables

Measure	Platelet count	Bleeding Severity	Emotion-SDQ	Conduct-SDQ	Total Difficulties - SDQ	Quality of Life KIT score	Total Fatigue	General Fatigue	Sleep Fatigue	Mental Fatigue
Inhibit	.05	-.18	.35	.67**	.75**	-.21	-.55**	-.38*	-.37*	-.68**
Shift	.17	-.20	.53**	.53**	.70**	-.22	-.67**	-.56**	-.59**	-.65**
Emotional control	.26	-.23	.47**	.66**	.64**	-.40*	-.50**	-.39*	-.42*	-.51**
Initiate	.16	-.43*	.35	.65**	.74**	-.14	-.47**	-.29	-.43*	-.50**
Working Memory	.20	-.16	.42*	.62**	.74**	-.18	-.71**	-.53**	-.45*	-.86**
Planning	.15	-.34	.39*	.57**	.67**	.08	-.51**	-.35	-.38*	-.60**
Organisation of Materials	-.24	-.01	.22	.35	.32	-.03	-.23	-.08	-.13	-.35
Monitor	.19	-.34	.27	.56**	.63**	-.01	-.37*	-.13	-.34	-.49**
Behaviour Regulation	.19	-.25	.50**	.75**	.81**	-.34	-.62**	-.46*	-.51**	-.68**
Meta- cognition	.12	-.31	.40*	.67**	.76**	-.09	-.53**	-.31	-.44*	-.63**
Global Executive Composite	.15	-.29	.46**	.73**	.81**	-.19	-.59**	-.38*	-.47**	-.68**

Note. BRIEF= Behaviour Rating Inventory of Executive Function; SDQ= Strengths and Difficulties Questionnaire. n varied between 30 and 31 due to missing data. Higher BRIEF scores indicate greater problems. High fatigue scores indicate lower problems with fatigue.

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).

### **3.6 Quality of life**

The mean score of self reported quality of life for children was 79.38 ( $SD = 14.55$ ). This score ranged between 39.4 and 95.2. The mean parent proxy ratings of child's quality of life was 78.19 ( $SD = 14.45$ ) and ranged between 51.9 and 99.0.

In exploratory analysis, variables associated with quality of life were examined. From the bivariate correlations (Tables 11-13) we can see that several variables were associated with quality of life. For parents' ratings (Tables 11 & 14) this included Total Difficulties with emotional/behavioural functioning (SDQ), Emotional Symptoms (SDQ), and Emotional control (BRIEF). For child ratings, variables associated with quality of life included Emotional Symptoms (SDQ), and general, mental and total fatigue scores (Tables 12 & 13).

### **3.7 Appraisal**

#### **3.7.1 Associations between appraisal items (Table 15).**

In addition to the research question concerning appraisal, the characteristics of appraisal as related between parent and child were examined. Parent and child ratings of severity of illness correlated with each other, but were significantly different from each other ( $t(30) = 2.972, p = .006$ ), with children rating their condition as less severe than their parents. Both parents and children's rating of severity of condition correlated with their ratings of the amount their life was affected. Parents rated their own life as more affected

if their child's life was more affected. Parent's perceived ability to cope was associated with their report of their child's ability to cope. For parents, appraised severity was significantly negatively correlated with their appraisal of their own ability to cope. This was not the case for children; severity rating did not correlate with coping ability. Child's rating of the severity of their illness was positively correlated with the amount their life had been affected.

Table 15: Association between appraisal items

Measure	Parent ratings					Child ratings		
	Severity	Childs life affected	Own life affected	Own coping	Ability to cope	Severity	Life affected	Ability to cope
<b>Parent's ratings</b>								
Severity	-							
Child's life affected	.70**	-						
n	34							
Own life affected	.46**	.61**	-					
n	34	34						
Own coping	-.56**	-.48**	-.45**	-				
n	34	34	34					
Child's ability to cope	-.28	-.24	-.12	.53**	-			
n	34	34	34	34				
<b>Child's ratings</b>								
Child's severity	.37*	.22	.084	-.076	.002	-		
n	31	31	31	31	31			
Life affected	.44*	.34	.15	-.24	-.046	.76**	-	
n	23	23	23	23	23	25		
Ability to cope	-.29	-.54**	-.22	.28	.17	-.22	-.19	-
n	23	23	23	23	23	25	25	

\*. Correlation is significant at the 0.05 level (2-tailed)

\*\* . Correlation is significant at the 0.01 level (2-tailed).

### **3.7.2 Associations of appraisal with adjustment.**

Each appraisal aspect (severity, affected life, and coping ability) is reported in turn. To answer the fourth research question, concerning appraisal and adjustment, each appraisal item was correlated with each adjustment item (fatigue, executive functioning, emotional and behavioural functioning, and quality of life). Some additional analyses were carried out between the three sources of severity rating, as each one was thought to contribute meaningful data and their association would assist in interpreting the other results.

Table 16: Bivariate correlations (Pearson's r) of parent appraisal ratings with other variables

	Platelet count	Bleed severity	SDQ- Emotion	SDQ- Conduct	SDQ- Total Difficulties	KIT summary score	Fatigue Total	General Fatigue	Sleep Fatigue	Mental Fatigue
Severity	.13	.30	-.01	.11	.13	-.31	-.33	-.40*	-.26	-.20
Child's life affected	.11	.24	.16	.39*	.44**	-.47**	-.42*	-.36*	-.28	-.41*
Own life affected	.14	.018	.11	.42*	.32	-.30	-.41*	-.32	-.22	-.45**
Own ability to cope	-.01	-.19	-.24	-.26	-.23	.53**	.12	.16	.05	.09
Child's ability to cope	-.01	.12	-.17	-.24	-.20	.45**	.02	-.01	-.02	.06

*Note.* *N* values varied between 32-34, due to missing data. SDQ = Strengths and Difficulties Questionnaire. KIT = Kid's ITP Tools (quality of life scale)

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).

Table 17: Bivariate correlations (Pearson's r) of child appraisal ratings with other variables

		KIT									
Measure		Platelet count	Bleeding severity	SDQ- Emotion	SDQ- Conduct	SDQ- Total Difficulties	summary score	Fatigue Total	General Fatigue	Sleep Fatigue	Mental Fatigue
Severity	r	-.03	-.07	.43	.31	.36	-.58**	-.51**	-.52**	-.44**	-.33
	N	34	34	16	16	16	24	34	33	34	34
Life affected	r	.34	-.08	.40	.22	.31	-.44*	-.63**	-.49*	-.59**	-.50*
	N	25	25	16	16	16	24	25	25	25	25
Ability to cope	r	.31	-.41*	-.31	.23	.08	.36	.20	.18	.07	.22
	N	25	25	16	16	16	24	25	25	25	25

Note. KIT = Kid's ITP Tools (Quality of life scale)

\*. Correlation is significant at the 0.05 level (2-tailed). \*\*. Correlation is significant at the 0.01 level (2-tailed).

### **Severity.**

Clinicians mean rating of severity of illness was 1.28, compared with 2.82 as rated by parents and 1.94 for child ratings. There was a significant correlation between clinician rating and both parent ( $r(32) = 0.622, p < .001$ ) and child ratings ( $r(32) = 0.658, p < .001$ ). This indicates that high ratings from clinicians corresponded with high ratings from the other raters. However, clinicians' ratings were significantly lower than parent ratings ( $t(33) = -8.712, p < .001$ ) and child ratings ( $t(33) = -2.878, p = .007$ ). Neither platelet count nor bleeding severity correlated with any of the three subjective ratings of severity.

Parent's rating of severity correlated with one fatigue subscale, general fatigue, indicating the more severe the condition was rated, the worse the general fatigue levels (Table 16). Child's rating of the severity of their illness, negatively correlated with their general, sleep and total fatigue scores, indicating those that reported a more severe condition also reported more problems with fatigue (Table 17). For children, their rating of their quality of life was negatively correlated with the perceived severity of their illness, with a more severe illness equating to a poorer quality of life.

### **Life affected.**

As seen in Table 16, parents rated their own life as more affected if their child had greater conduct problems, higher total and mental fatigue and greater problems with emotional control ( $r(28) = .40, p = 0.03$ ), and working



memory ( $r(28) = .45, p = 0.01$ ). Parents' rating of the amount their child's life is affected correlated with the same measures and, in addition, general fatigue. For parents, quality of life for their children was associated with the amount child's life was affected. Child's rating of the amount their life was affected by their condition correlated with Emotional Symptoms (SDQ), total fatigue and all three fatigue subscales (Table 16). Child-rated quality of life was also associated with the amount their life was affected.

### ***Ability to cope.***

Parents rated quality of life for their child was better when they perceived higher coping ability in themselves and in their child (Table 15). Children with lower bleeding severities, reported being more able to cope (Table 16).

In summary, as all appraisal variables were associated with at least one adjustment variable, related to the fourth research question.

### **3.8 Qualitative comments**

Additional comments in the questionnaire packs gave support to the research questions examined above about the psychological adjustment profile of children with ITP. Several issues were presented in the qualitative comments from the KIT and the VAS measures. Parents reported that they were bothered by the uncertainty around the illness and its prognosis, its risk management (including restricting activities), and its visual appearance.

Parents commented that they thought the issues that affected their children were the blood tests, the anxiety around the condition, specific physical complaints, and isolation from friends. Some comments from parents commented on how the situation at present was more positive than it had been previously, which reflects the changeable nature of the condition. Themes from child comments concerned being bothered by restricted activities, anxiety around the time-course and prognosis of the illness, and blood tests.

#### **4. Discussion**

This study aimed to address gaps in the literature regarding the psychological profile of immune thrombocytopenia (ITP) in children. There has been recent interest in the quality of life for children with this condition (E.g., Klaassen et al., 2007) but knowledge about other adjustment variables remains scarce, despite requests for their investigation. There have been a limited number of studies in adults with ITP but as the condition presents quite differently in children and adults (Schulze & Gaedicke, 2011), it is important to investigate these populations separately. This study examined emotional-behavioural functioning, fatigue and executive functioning as adjustment variables and investigated the relationships between these variables with quality of life and factors associated with the condition (platelet count and bleeding severity). The first main research question concerned the adjustment profile for children with ITP compared with a 'healthy' sample of children, without the condition. As previous studies regarding associations between clinical factors and

adjustment have been mixed (Wallander & Varni, 1998) but considering research with the field of ITP (Newton et al., 2011), one of the research questions addressed whether this association would be observed in children with ITP. Another research question concerned the relationship between adjustment variables, similar to known links between mood, fatigue and thinking skills (Fleming et al., 2004; Goretti et al., 2012; Swain, 2000). Finally, this study introduced the construct of appraisal and investigated its influence on adjustment outcome. In relation to background literature for other paediatric conditions the final research question concerned whether, within the sample, more positive appraisal would be related to better adjustment. Each of these research questions are discussed in turn, including dissection of each adjustment variable, with implications of the findings, then the study is evaluated in terms of its strengths and weaknesses and conclusions are presented.

## **4.1 Main findings**

### **4.1.1 Emotional-behavioural functioning.**

The first adjustment variable examined was emotional and behavioural functioning. Most children were rated by the parents to have no significant problems with emotional and behavioural functioning. Additionally, children did not rate their functioning as worse compared with children without ITP. However, parents rated their children with ITP as having significantly higher rates of emotional symptoms compared to the general child population. This is consistent with previous research literature that has shown some increased

risk for psychological problems for children with chronic health conditions (Barlow & Ellard, 2005) and findings of higher rates of emotional symptoms (anxiety and depression) in children with other blood disorders (Yang et al., 1994). Anxiety and distress were additionally mentioned by parents and children in their qualitative comments in the current study. However, as children and parents differed in their ratings, caution should be applied when making conclusions about the level of difficulties for this group. It cannot be ruled out that parental well-being, not measured in this study, was influencing their judgements.

It is possible that the presence of ITP affects mood in the way that the presence of any chronic health condition might. For example, the burden of hospital appointments and anxiety around the condition might be expected to be similar to other conditions. However, issues specific to ITP, such as restricted activity, potential for increased anxiety given the uncertainty about the condition and the visibility of condition may additionally affect mood. Indeed some of these issues were highlighted by comments from parents and children (see below). Previous research in children with chronic health conditions found that activity restriction mediates the relationship between illness characteristics and depression (Walters & Williamson, 1999). There may also be a biological mechanism underlying mood difficulties, such as the role of platelets as discussed below.

Parental ratings for behaviour (or conduct) problems were higher for children with ITP compared with the normal population, and this difference approached significance ( $p= 0.051$ ). Although some literature shows that

behavioural problems are more common in children with health conditions (Pinquart & Shen, 2011), including blood disorders such as haemophilia (Trzepacz et al., 2003) and conditions that are considered medically benign (Connolly et al., 2006), most literature also concludes that the majority of children are not at increased risk of emotional or behavioural problems (e.g. Trzepacz et al., 2003).

#### **4.1.2 Fatigue.**

In answer to the research question, both children and their parents rated child fatigue as significantly worse compared with a sample of children without ITP. This supports results from surveys (Sarpatwari et al., 2010), focus groups (Barnard et al., 2003) and anecdotal reports from haematology professionals that fatigue is a significant symptom for children with ITP. However, there was considerable spread of fatigue scores, indicating that many children may have had little to no problem with fatigue. There is also no cut-off score for the measure used, to determine the severity of the scores.

This is the first study to explore fatigue using a standardised quantitative fatigue measure for this group. Fatigue scores were also compared with those for children with sickle cell disease (SCD), but this produced mixed findings. Parents' ratings of child fatigue levels were not significantly different with the SCD comparison group, whereas children reported fewer problems with fatigue compared to children with sickle cell disease. As fatigue is a subjective construct child ratings may be considered to be the 'best' ratings, although these are subject to self-report biases. In addition, the sample of

children with sickle cell used for comparison used a slightly larger age range, including older children up to the age of 18. As our current study found that older children had greater problems with fatigue this may have been an influence in the comparison sample.

Fatigue can be affected by steroid treatment (Provan et al., 2010), but as no children in this sample were receiving steroid treatment at the time of the study, this indicates other mechanisms are operating. Possible biological mechanisms for fatigue in ITP include general psychological stress, possibly mediated through Corticotrophin-releasing hormone (CRH) (Swain, 2000), through serotonin or other biological effects affected by reduced platelet count/abnormal auto-immune response (Hill & Newland, 2015), due to elevated levels of inflammatory cytokines (Kistanguri & McCrae, 2013; Swain, 2000) or through oxidative stress processes (Kamhieh-Milz & Salama, 2014). It is also possible that fatigue was related to other co-morbid health conditions (Newton et al., 2011), to low mood (Swain, 2000), reduced activity/exercise (Lewis & Wessley, 1992), or low self-efficacy (Riemsma et al., 1998) as found in other studies.

Fatigue may be related to toxicity of treatments (Zehnder et al., 2010). Despite none of the children in this study being currently on steroid treatment, there was a difference in the levels for those on treatment compared with those who were not. This may indicate side effects of these treatments, or may reflect the severity of the condition that warranted treatment

commencement. In treatment studies for adults with ITP, fatigue has been reported as an adverse side effect for some treatments (Kuter et al, 2013) and longitudinal treatment studies have failed to improve levels of fatigue, despite improvements in other quality of life domains (Kuter et al., 2010). Increase in fatigue may have knock-on effects such as problems with academic functioning, engagement with social and leisure activities (McCabe, 2009) and it is therefore an important variable to investigate.

#### **4.1.3 Executive function.**

Executive functioning was used as another measure of adjustment and the research questions concerned whether this would be worse for children with ITP compared with a healthy population. It has been recognised that the cognitive profile of children with ITP has been under-researched and recommendations have been made that this should be an area of research focus (Cooper, 2014). This study is the first to investigate executive function in children with ITP, and contributes to understanding the cognitive profile for this group.

Overall executive functioning (as measured by the Global Executive Composite and Behaviour Regulation scales of the BRIEF) and Emotional Control was significantly worse compared with a normative group. Although, almost 20% of this sample of children with ITP had a high level of problems with overall executive functioning and in the normal population only 6.6% would be expected to have scores within this range, this still represents that

the majority of children in this study (80%) had no significant difficulties with executive function. These results remain tentative given the sample size and other limitations of the study. It should be stated again that in this study executive functioning of the children was ascertained through parent report, which may provide different results to formal cognitive testing. If a finding of increased prevalence executive functioning difficulties for children with ITP was supported through further research, it remains likely that the majority of children would experience no difficulty. There were no significant differences on the BRIEF between this sample of children with ITP and a comparison study of children with sickle cell disease. However, these results should be viewed with caution given the small sample sizes in the current study and the comparison sample.

It is unclear whether any biological mechanism contributes to executive functioning difficulties. These could be explored in future research if findings with regard to executive functioning difficulties were verified. An alternative explanation would be that executive functions, such as ability to organise oneself may be affected by missing school which may provide a context for developing these skills. As none of the children were currently on steroid treatment, the cognitive effects reported are mostly likely to be due to other factors, although previous steroid use was not investigated in this study. Finally, executive function changes may be related to the other adjustment variables, as discussed below.



#### **4.1.4 Quality of life.**

Quality of life could not be used as an adjustment variable in the same way to compare to other child populations as it is an ITP-specific measure. However, its inclusion in the current study provided information about how other factors related to quality of life within this condition, as discussed below. Average quality of life (QoL) scores were comparable to other studies of children with ITP using the same measure (Flores et al., 2013; Klaassen et al., 2013). However, there was considerable variation in QoL scores. For example, child ratings varied from as low as 39.4 to 95.2/100. This emphasises this variability in quality of life across this sample, and parallels the patterns observed across a wider population of children with ITP.

#### **4.2 Association between adjustment variables**

This study found a significant relationship between adjustment variables of executive function, fatigue and mood. The association between mood and executive function is in line with research in adults with depression (Chepenik et al., 2007) and for anxious-depressed boys (Emerson et al., 2004). The association between fatigue and mood in this study was in line with findings across paediatric literatures (as reviewed by Swain, 2000). Fatigue is an under-researched area in children (McCabe, 2009). In relation to this, literature relating to fatigue and executive functioning is scarce. However, the association between these two variables is in keeping with a recent study for children with MS, who had poorer performance on executive function tests if reported to be cognitively fatigued (Goretti et al., 2012). Very

few studies have examined these three variables in the same study and in this way this study benefits from their simultaneous examination.

Children's quality of life scores were significantly related to child emotional symptoms, for both parent and child ratings. Other studies have found an association between emotional symptom scores and quality of life (Tracy, Dechant, Sperling, Cho, & Glosser, 2007) and a possible role for emotions moderating the effect of functioning ability, or disability status, on quality of life (Janssens et al., 2003).

This association could be due to the inclusion of mood items in the QoL scale and some researchers have stated that mental health factors should not dominate quality of life measures (Tracey et al., 2007). The quality of life measure that was used in this study has only three items which directly address mood (i.e., 'I felt cranky', 'I felt upset', 'I felt anxious') but also additional items assessing somatic symptoms and some items that asked about specific worries (e.g., 'I worried about my platelet count'). Other items asked about children being 'bothered' by events or aspects of the condition (e.g., 'I was bothered that I could not do anything to get better') and it is not clear how much this phrasing overlaps with constructs of mental health.

For parent ratings, scores for emotional-behavioural functioning (Total Difficulties on the SDQ), and Emotional Control (BRIEF) were related to child's quality of life. This may indicate that quality of life ratings as made by

parents are based mostly on observable symptoms. From the child's perspective, general, mental and total fatigue scores were related to quality of life. Only one item of the KIT directly asks about tiredness so this is likely to be a genuine association rather than just construct overlap. This finding replicates findings reviewed for fatigue and quality of life in children with chronic health conditions (Eddy & Cruz, 2007).

#### **4.3 Association of clinical measures with adjustment**

Informed by the risk and resistance model, one of the research questions addressed whether clinical features of ITP, including platelet count and bleeding severity would be related to adjustment. There was no association between clinical factors and poorer emotion-behavioural functioning, fatigue or executive functioning (apart from one subscale).

Platelets have a role in transportation of serotonin (Berger et al., 2009), and therefore increased destruction/reduced production of platelets may affect these neurotransmitter levels, which would affect mood regulation. Although there was no correlation between platelet count and emotional symptoms in this study, all children had had altered platelet counts in the last six months. Once below  $150 \times 10^3$  platelets per micro litre (mCL), smaller variations may not make a difference. It would be interesting to know whether comparing platelet counts in the normal range compared with the current sample would find an association.

This study found that higher bleeding severity was related to fewer behavioural problems. At first this result seems perplexing. It is not possible from this study to explain this finding but it may be that caring behaviours from parents increase with more observable bleeding and this in turn may reduce behavioural problems. Alternatively, children who are less ill (low bleeding severity) may feel more able to 'act out' against unwanted restrictions on their activity and attending hospital appointments. Also, at higher bleeding severities, treatment may be more readily considered and delivered. Although the relationship between bleeding and treatment was not examined in this study, this may provide conflicting results as treatment may be initiated for those with high bleeding severity but being on treatment may keep bleeding severity down. Also this would not account for previous treatments, and their duration and their potential effects over time on conduct, even if discontinued.

In answer to the third research question, the current study found no relationship between either platelet count or bleeding severity with fatigue and only one executive function subscale was associated with bleeding severity. This is in contrast to the results for fatigue in adults reported by Newton et al. (2011). However, there are some studies in adults which had similar findings (Sarpatwari et al., 2010; Zhou et al., 2007). In other blood disorders, deficits in cognitive problems are related to some measures of condition severity, such as intracranial haemorrhage and anaemia (Hijmans et al., 2011; Morales et al., 2013), but results from the current show no association with condition

severity as measured by platelet count and bleeding severity on the whole with executive functioning.

Finally, neither platelet count nor bleeding severity was associated with quality of life. This replicated the finding of Neunert et al., (2009) who also found no relationship between these measures. This indicates that other factors associated with the condition, beyond clinical severity may be impacting on children's lives.

#### **4.4 Appraisal**

The final research question concerned the role of appraisal and adjustment. Appraisal has been shown to be related to outcome in chronic health conditions (e.g., Guion & Mrug, 2012). This is the first study to incorporate a measure of appraisal in examining adjustment outcome in ITP. The three areas that were addressed in the bespoke visual analogue appraisal measure (VAS) are discussed below. Results should be viewed with caution considering the novelty of the measure.

##### **Severity.**

Parents, children and clinicians differed on their severity rating of ITP, with clinicians rating it as the least severe, then children, and parents giving it the highest severity rating. Clinicians would have based their ratings on blood counts and bleeding symptoms, infrequent presentations of the child to clinic and reports from families. They may not have insight to the range of

psychosocial factors that may influence perceived severity for parents and families. Research on subjective severity ratings for children with sickle cell disease found that clinicians were more likely to rate the condition as less severe than parents and children when objective clinical measures indicated a less severe disease (Connelly, Wagner, Brown, Rittle, & Cloues, 2005). Alternatively, families may have misunderstood the severity of the condition. This has important implications for clinical dialogue between clinicians and families to ensure that clinicians are aware of all symptoms and parental or child concerns and wherever appropriate, to try to reassure parents and children when the condition is in fact relatively mild. This finding parallels reports from the adult ITP literature, where discrepancies in perceptions about medication side effects between clinicians and patients were found (Guidry et al., 2009).

The finding that children rated their condition as less severe than their parents parallels similar findings for children with sickle cell disease (Connelly et al., 2005). Children, particularly young children, may not know extensive details about their condition, which may influence their ratings. Alternatively, parents may rate the condition higher in severity if they are not adjusting well to their child's condition (Connelly, et al. 2005), which was not examined in this current study. These results emphasise the utility of multiple reports.

Neither platelet count nor bleeding severity was significantly correlated with any of the three subjective ratings of severity and only child severity ratings,

not condition factors, were related to child's quality of life. These findings support the finding that perceived severity of a health condition is a subjective measure, which is not necessarily related to objective clinical measures of severity, as has also been reported for sickle cell disease (Barakat et al., 2006)

### **Ability to cope.**

Children with lower levels of bleeding severity reported being more able to cope with their condition. One possible explanation for this is that the bleeding severity scale incorporates presence of bruising and this result suggests that observable symptoms may affect coping ability. It may be if more severe bleeding occurs it may be observed by others which would have social consequences. However, it may also be individual management of bleeding that is hard. For instance, heavy periods were mentioned as a concern by children and parents.

Parents perceived a better quality of life for their child when they and their child could cope with the condition. However, it may be that a better quality of life led to a perception of better coping. As this was a cross-sectional correlation, causality cannot be inferred. This finding has been observed in other paediatric conditions. For instance, for children with cancer, perceived ability to enact coping strategies was related to better quality of life (Cunningham et al., 1991).

### **Life affected.**

As might be expected, parents rated their lives as more affected if their children's lives were more affected. Parents not only have to deal with the psychological consequences of a condition on children but also the practicalities of monitoring and treatment, such as attending hospital appointments. Parents reported that their own life was affected if children displayed particular adjustment difficulties, including behaviour, working memory and fatigue difficulties. This is related to literature that shows a similar relationship between reported impact and greater behavioural and cognitive problems, in a study of children with epilepsy (Camfield et al., 2001). Parental well-being was not specifically examined in this study but should be considered in paediatric settings.

Some, but not all, of the appraisal ratings were related to quality of life. In addition to associations discussed above, appraisal scores also related to other adjustment variables including fatigue, conduct (parent ratings), and emotional symptoms (child ratings). In each case, more positive appraisal ratings, including higher perceived coping ability, and lower rating of life being affected by the condition, was associated with better outcome on these adjustment variables. Therefore, there was some evidence that a more positive appraisal would be associated with better adjustment. The relationship between appraisal and adjustment outcomes is likely to be a complex one. For instance, it is not clear whether children and their parents were predisposed to particular appraisals, or whether positive or negative



outcomes of the condition changed their view on their appraisal of the illness. As items from the VAS appraisal measure correlated with more of the adjustment outcomes than platelet count, it may be important to examine appraisal, and stress processing more broadly, in future studies.

#### **4.5 Qualitative comments**

Although not a focus of this study, the written comments provided by children and families provided richness to the data and supported quantitative findings. Several comments were made by parents and children about restriction on physical activities. The frequency of comments about activity restriction was surprising given that this is not usually advised by clinicians except in the first 12 months of the condition when platelet count is particularly low (Blanchette & Bolton–Maggs, 2010). Given the rarity of the condition, general practitioners or paediatricians may not be as familiar with the guidelines for lifestyle management and therefore unnecessarily suggest a restriction in physical activities. As many of the children had been seen for a long time at the specialist centres where they were approached for the study, this is unlikely to be the case in the current cohort, although cannot be ruled out as having occurred in the past. It may also be that parents and children choose to take a ‘better safe than sorry’ approach and limit activity despite clinical recommendations. Children also commented that they felt isolated from friends, and it is not clear whether this was related to activity restriction (physically isolated) or due to being perceived as different (psychologically isolated).

Both parents and children were bothered by the uncertainty around the illness. Unknown cause and aetiology, multiple treatment options, the 'watch and wait' approach and unknown prognosis/chance for spontaneous remission are specific to ITP and likely contribute to anxiety. This is related to research literature for other conditions that suggest that increased uncertainty is associated with poor psychological outcomes for children (Hoff et al., 2002).

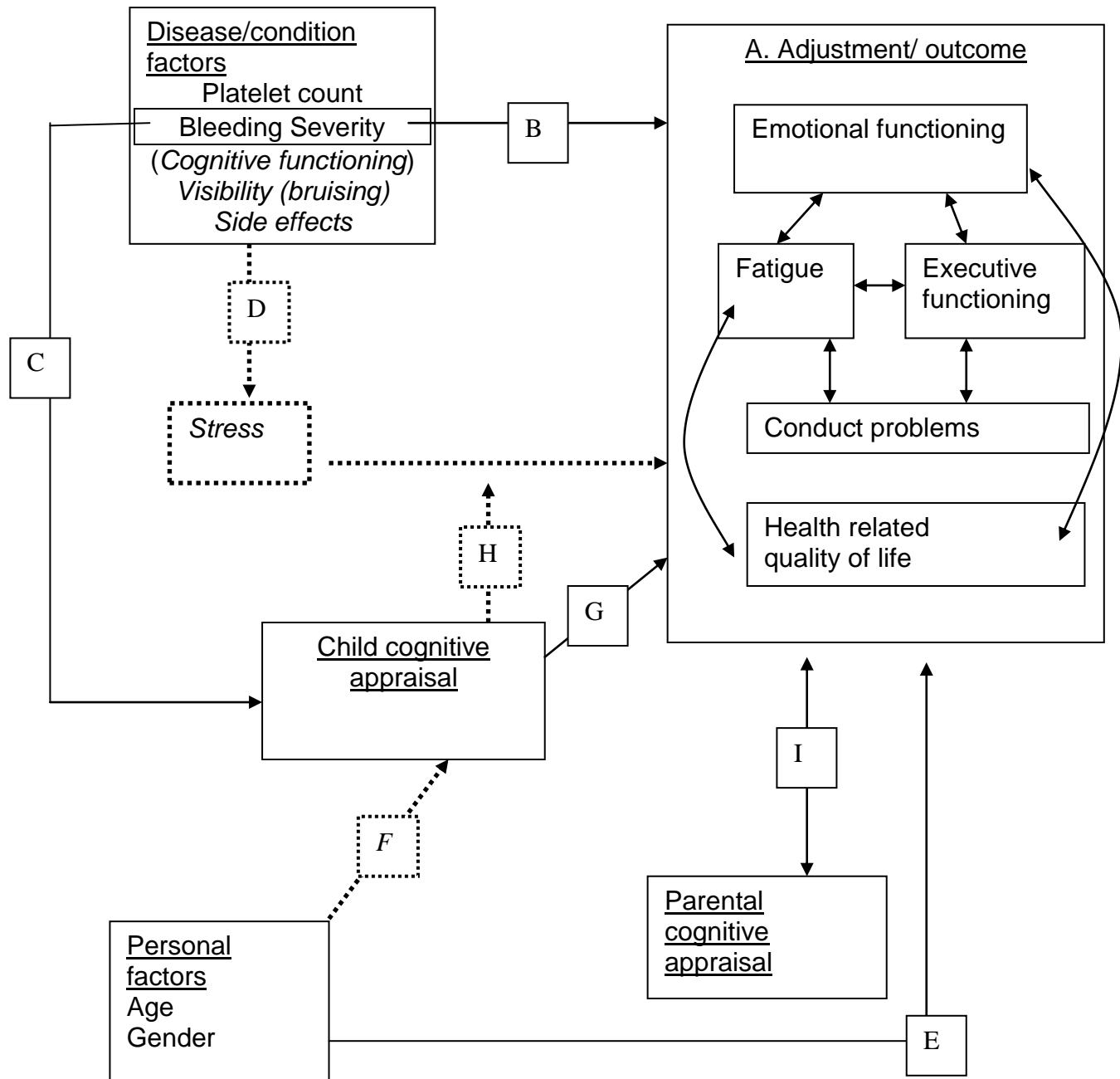
Finally, blood tests were an issue for children despite anaesthetic creams being used and despite children's familiarity with the procedure. Although a necessary part of ITP monitoring, the effect of this procedure on children should not be underestimated and additional steps to alleviate anxiety should be considered, which might include targeted psychological intervention around needle phobia and procedural anxiety.

Finally, comments were also made about visible signs of the condition, mainly bruises, although it is not clear what bothered them about these. For instance, whether they were worried about appearance or whether these visible signs acted as a reminder about other potential ongoing effects of the illness. In literature regarding children with chronic conditions, body image concerns are known to be related to measures of well-being (Wolman, Resnick, Harris, & Blum, 1994). However, this may also depend on the appraisal and meaning given to the visibility of the symptoms.

#### **4.6 Theoretical implications**

This study advances knowledge in areas where there were significant gaps about the psychological profile of children with ITP. It adds to current understanding about fatigue, emotional and behavioural difficulties and executive function difficulties, using standardised measures, which have not previously been used for children with ITP. Theoretical models have not been used to date to help understand adjustment in ITP. The design of this study meant it was not possible to test particular elements of the risk and resistance model (Wallander & Varni, 1992). Nevertheless, the model provides a useful framework for considering how aspects of the condition fit together. Figure 5 shows a suggested adaptation to the model, including variables investigated in this study as well as gaps remaining, for further research. To reiterate, not all links shown in the figure were explored in the current study and the results, particularly the inter-relationships between variables highlight the complexity and limitations of the model, as discussed further below.

Figure 5: Adapted Risk and Resistance model for ITP



Note. Dashed lines and italicised variables indicate pathways suggested in the original risk and resistance model (Wallander and Varni (1992), but not explored in the current study. Solid lines indicate associations explored in the current study.

The primary aim of this study was to understand the adjustment profile for children with ITP. Increased rates of adjustment difficulties, as measured by total emotional and behavioural problems, emotional symptoms specifically, and fatigue problems, were found in this sample and these have been added to the diagram (Box A). Again, it is important to emphasise that although there were higher proportions of children experiencing difficulties in these domains, a large proportion of children were reported to experience no significant difficulties. This study found evidence that executive functioning may be affected in children with ITP. It is not clear from this study whether these difficulties should be included under the model as a characteristic of ITP or as an outcome, or both, and it is likely that this would not apply to all children with the condition. It may be that broad cognitive changes occur that relate to changes in brain blood flow or other biological mechanisms whilst more specific effects on cognition (e.g., executive functioning) are exacerbated by difficulties in fatigue and mood.

The risk and resistance model has been criticised for failing to define relationships between variables (Holmbeck, 1997). Related to this, the original model does not discuss the potential interrelationships between adjustment variables. This current study found that there were significant associations between adjustment variables. Lines have been added to indicate these (Figure 5, Box A). These indicate associations between executive function, fatigue and emotional functioning, conduct problems as related to fatigue and executive functioning and quality of life related to

fatigue and emotional functioning. Conduct and executive functioning are not linked in the diagram to quality of life, in line with current findings. Two-way arrows have been used in the diagram as this study did not provide information as to the direction of these relationships. Further research is required to test these relationships.

It is difficult to encompass the role of condition factors in to the model, given the current findings. Platelet count did not seem to be directly related to adjustment variables, although this has been kept in the model as it is not clear whether this might affect other variables that were not studied. It is possible that platelet count may not be a good clinical marker and general representation of the illness. The relationship of bleeding severity to adjustment is indicated by Line B, but this does not represent a link to all variables. It represents association with one subscale of BRIEF and child quality of life as rated by parents. It also related to conduct as rated by children although in the unexpected direction of higher bleeding related to fewer behaviour problems, as discussed above. Again, it may be that bleeding severity influences other variables through indirect pathways. Results from this study support a pathway linking bleeding severity to child's appraisal (Line C), as children perceived they could cope better when they had lower bleeding severities. This direct link is not suggested in the original model (Wallander & Varni, 1992).

The original model suggests that condition factors have not only direct effects on adjustment, but also mediated effects through stress (Pathway D). Generic daily stress, condition related stressors and significant life events have been shown to effect a person's adjustment (Casey et al., 2000; Coker et al., 2011; Perrin et al., 1996) and mediate the relationship between physical symptoms and adjustment (Casey et al., 2000). Due to mixed results for direct effects of condition factors on adjustment, it seems important to investigate indirect routes that these variables could be operating in individuals with ITP.

Side effects of treatment and visibility of condition are suggested in the original model and although not investigated in the current study were important to add. 'Side effects' were added as toxicity of treatments has been a highlighted issue for children with ITP (Zehnder et al., 2010). 'Visibility' has also been added as its role is supported by Varni and Setoguchi's (1991) research that shows that higher perceived physical appearance was related to better outcome in terms of anxiety and depression scores. However, the important term here is 'perceived' and it has been suggested that subjective rather than objective appearance and the appraisal on this is what affects outcome (Varni & Setoguchi, 1996). As bleeding severity as used here considered observable signs of bleeding, this measure may be related to visibility and warrants further study.

It is difficult to draw clear conclusions about the association between gender and age with outcome as there were mixed results in the study and only

examined in brief. Largely, age and gender were not related to adjustment variables. The exceptions to this were for age and emotional problems and for age and gender with executive functioning. There was also a trend association between age and fatigue, with older children reporting greater difficulties. Therefore this has been tentatively added as a line to the model (line E), to represent that an association may exist for certain variables. The original model proposes that personal characteristics, including age and gender would influence child appraisals (Wallander & Varni, 1992) (Line F). For instance, some studies have shown that girls may perceive stressors as more severe (Walker, 2007). The influence of age and gender on appraisal was not examined in this study.

A direct line (line G) has been added to the model to show the link between child appraisal and adjustment. This represents two of the appraisal domains being related to quality of life and fatigue and one appraisal domain related to emotional symptoms. Children's ratings of their ability to cope were not related to adjustment outcomes and this item may not have been accessing the same overall construct as indicated by internal consistency analysis of the appraisal measure. As proposed in the original model, there is a possible moderating effect for cognitive appraisal between other variables. This was not investigated in this study but would be important if investigating appraisals further for this population, and is represented by pathway H.



Although not considered directly in the original model, there is a hypothesised indirect association between parental appraisal and child adjustment (Hocking & Lochman, 2005; Wallander & Varni, 1992). Other literature has examined these associations. For instance, perceived impact, perceived ability to cope and appraised threat of a condition as rated by parents have all been shown to be associated with poor outcomes in children (Camfield, Breau & Camfield, 2001; Sales, et al., 2008; Stuber et al., 1997). In the current study, there was association between parents' appraisal with several adjustment domains, including conduct problems, emotional control, and fatigue (this is signified by Line I). Although it is not possible from this study to determine the direction of this relationship, conceptually it would make sense if parents' lives were affected by adjustment problems rather than adjustment problems increased if parents' lives were more affected. Generally, parent and child appraisals in the same domain (i.e., impact, severity, ability to cope) were not related.

Although adults and children with ITP have different presentations and time course of the illness (Schulze & Gaedicke, 2011), similar psychological outcomes, such as difficulties with fatigue are reported for both groups (e.g., Sarpatwari et al., 2010). Research into adults with ITP has started to consider the theoretical links between variables (Mathias et al., 2008) but may also benefit from considering the model proposed above. Furthermore, it is likely that associations between variables investigated in this study and proposed in the model above would be common across disorders (Stein & Jessop, 1982)

and therefore this research also adds to an understanding of paediatric conditions as a whole.

#### **4.7 Clinical implications**

It is suggested that a range of factors should be considered in treatment decisions for children with ITP (Buchanan & Adix, 2001). This research highlights to clinicians the secondary (psychological) characteristics of ITP present in some children with ITP, which up until this point, were suspected but unverified. These may influence treatment decisions as paediatric healthcare provision should support the holistic presentation of the child. Also, beyond treatment of the ITP itself, clinicians may want to additionally screen for and treat psychological issues, which may result in better outcomes for children experiencing difficulties. Furthermore, there is some evidence to suggest that in haemophilia, stress may actually bring on bleeding events (Mattson & Gross, 1966; Perrin et al., 1996). It is unknown whether there exists any similar pattern for ITP, but it is plausible that similar mechanisms may be operating. Therefore, detecting and addressing psychological difficulties may even provide an indirect non-invasive treatment for bleeding symptoms.

This study demonstrates that fatigue is a significant problem for some children with ITP. A clinical implication of this is that fatigue symptoms should be routinely asked about in ITP clinics and appropriate support provided, as necessary. This may include CBT interventions that have been effective in

reducing fatigue in other conditions (Gielissen, Verhagen, & Bleijenberg, 2007; Knoop, Stulemeijer, de Jong, Fiselier, & Bleijenberg, 2008). As increasing physical activity is effective at reducing fatigue (Koornstra, Peters, Donofrio, van den Borne, & de Jong et al., 2014), conversation needs to take place between clinicians and families about the balance in risk management of internal bleeding from activity-related injury versus the benefits of activity, on an individual case basis.

Recently, it has been suggested that in order to better support those with ITP and fatigue there needs to be a greater understanding of the treatable causes of fatigue, such as mood disorder (Hill & Newland, 2015). This study provides evidence of association between fatigue and mood problems in ITP. This would suggest that both direct interventions for fatigue, such as sleep hygiene, and interventions for mood may be effective in reducing fatigue.

Although results from the current study indicate that child fatigue, at least as rated by parents, is worse for those on treatment, it cannot be established whether the fatigue is due to treatment or whether children were experiencing significant levels of fatigue along with other symptoms that warranted treatment commencement. If the former, this could influence decisions about whether to start treatment.

As parents reported that certain adjustment characteristics of their children, such as fatigue, conduct and some executive domains, significantly affected

their own lives, parental well-being should be considered when these issues are highlighted in clinical settings for children with ITP. Parents and children may also benefit from having a better understanding of the condition, its mechanisms and the recommendations around activity restriction. This may be achieved through conversation with the clinician but also reflects that the clinical research in understanding ITP is still developing.

#### **4.8 Strengths and Limitations**

This study had several strengths. This was the first study to investigate psychological adjustment in children with ITP. Furthermore, it benefited from using standardised measures and multiple (self and informant) reports. It also enhanced the literature regarding the relationships between variables as these were examined simultaneously.

All parents and children approached agreed to take part in the study and took questionnaires. Although, some questionnaires were then not returned, this initial response indicated that the study was in principle acceptable to families. Beyond this, parents were keen for this research to take place and often asked follow up questions whilst the study was being introduced. As participants were asked to report at a single time point only, this meant that demand on participants was low.

The study benefitted from recruiting a sample that had a good spread of children across the age range and had an approximately equal mix of girls

and boys. This sample was felt to be generally representative of the wider child ITP population. However, it should be noted that children were seen at hospital sites with specialist haematology services. Whilst this would not have affected the age or gender characteristics, the sample may reflect more long-standing or complex ITP presentations. There was a large heterogeneity in the duration of the condition. Length of diagnosis was not investigated and so it is unclear what influence this may have had on the psychological profile of children, including whether difficulties were experienced more or less for children who had the condition for longer.

The study benefitted from using both child and parent proxy reports. Asking children themselves seems appropriate particularly in asking about subjective constructs such as fatigue. However, informant report may provide a more objective measure. In fact, each perspective is likely to be equally valid and allows a fuller understanding of the variables under investigation.

Other studies of fatigue have often combined or confounded sleep and fatigue and this study benefitted from the use of a measure that distinguished different types of fatigue (e.g., sleep fatigue). Isolating which areas children are experiencing difficulties may help tailor interventions and understand underlying mechanisms. However, it should be recognised that the definition and measurement of fatigue is still under development (McCabe, 2009)

By using the Behaviour Rating Inventory of Executive Function (Gioia et al., 2000a), it was possible to gain information from those that may know the children best. Neuropsychological testing would have increased the demand for child participants and may have resulted in a smaller sample size. However, the BRIEF should not be considered a replacement for cognitive tests as it is subject to report bias and measures different aspects of executive function (Anderson et al., 2002).

The main limitation of this study was that it was a cross-sectional correlational study. When considering associations between variables it was not possible to infer direction of influence. Longitudinal studies, including intervention studies, would be better suited to examine the impact of length of diagnosis and how changes in one variable impacts on the other variables.

The total sample for this study was 37 families and therefore only had the power to detect moderate or large effect sizes. A larger sample would have allowed for more complex statistical procedures, including analysis of multiple variables concurrently, for instance through a multiple regression sequence. This may have made it possible to look at mediation and moderation effects of different variables and larger samples would reduce effects of multicollinearity due to association between variables, increasingly the possibility to analyse the individual contribution of each variable. However, it is likely that variables such as fatigue, mood and executive function would always be

subject to these effects given their high degree of conceptual overlap and influence.

The visual analogue appraisal scale used in this study was a novel measure. This was constructed based on similar scales but intended to be shorter to give a snapshot of appraisal mechanisms that might be operating for this population. Authors have suggested that a single item or limited item scale may be just as valid as longer measures tapping similar constructs (Bowling, 2005). Tests conducted on this measure showed good reliability for the parent scale and for the child scale, if removing one item. However, further analysis into the validity and reliability of this measure was not carried out and therefore results should be viewed with caution.

From ad hoc discussion with one family completing the VAS measure with an interpreter, the parent commented that the question asking people to rate 'coping' on a scale was not a question you would ask within their culture or religion. The reason for this is that coping is assumed and considered more of an all-or-nothing construct. The parent and child still answered and understood the item but this indicates that further cross-cultural validation of this measure may be warranted.

Emotional symptoms were established from a five items, which incorporated a range of emotions. The Strengths and Difficulties Questionnaire (Goodman, 1997) was chosen for its brevity and, in parallel with other measures, gave a

snapshot of several variables at once. However, it sacrificed depth of knowledge and discrimination of emotional problems experienced. It was not possible to establish whether children were worried, depressed, experiencing other feelings, or a combination. Understanding the nature of the emotional symptoms would help tailor intervention but also help to better understand the different relationships between variables. For instance, it might be expected that anxiety might have a greater association with quality of life as measured by the KIT, as several items in the KIT measure ask about the extent that children are worried about aspects of their condition.

This study examined the association between outcome variables. This may illustrate the genuine relationship between these constructs. However, there was some overlap in measures. For instance, items on the cognitive fatigue measure (e.g., 'it is hard to keep my attention on things') would have overlapped with items from the BRIEF. Similarly, the KIT measure asked about problems with emotions. There are no subscales identified for the KIT measure, and its general factor structure is unclear. This study did not use a more standardised and generic measure of quality of life, such as the Pediatric Quality of Life Inventory<sup>TM</sup>, PedsQL<sup>TM</sup> (Varni, Seid & Kurtin, 2001), which also meant that comparisons could not be made with other paediatric populations in this domain.

Children were excluded if they had a co-morbid condition that was poorly controlled and was assessed as having the potential to significantly contribute



to symptoms. Eleven children in this study were allowed to participate with other conditions, made on clinical judgement in individual cases. Other conditions included, among others, diabetes, asthma, and undefined skin and gastrointestinal problems. Some children had multiple co-morbid conditions. In adults with ITP, where it was also decided not to exclude on the basis of co-morbid conditions, Newton et al. (2011) found that presence of co-morbid health conditions was a significant predictor of fatigue. It should be noted that, in that study, depression was also a co-morbid condition so it is not clear whether presence of physical, but not mental health, conditions would have had the same effects. The sample in the current study represents a realistic sample of children with ITP presenting to specialist national haematology service. Such co-morbidities perhaps provide support that there is some underlying systemic pathology in ITP (Frith et al., 2011). The sample was not large enough to test for differences between groups, therefore it was not clear the extent the results may have been affected by these conditions, compared with a sample of children with ITP and no other conditions.

Side effects of medications were reported from clinician and clinical notes. This relies on children and parents knowing about the side effects of the medications and reporting them through clinic appointments. It is possible that some of the observed effects of adjustment difficulties in this study may have been related to treatment effects.

This study aimed to capture the experience of patients as young as 5 years old through self report. For this the PedsQL™-Multidimensional Scale for Fatigue (Varni et al., 2002) was used as it has been developed and used for this age group. However, some of the younger children completing the measure (interviewed by researcher) seemed to struggle with the items. In particular, children struggled to answer the items that referred to 'trouble starting things' and 'trouble finishing things'. For this the researcher gave some prompts to aid completion. Although this may have affected responses, the researcher seeing families remained constant and therefore variations in verbal administration instructions remained limited. More generally, the questions often required children to simultaneously hold in mind the last couple of weeks, evaluate how frequently an internal state (feeling tired) had occurred, and rate how much of a problem it was for them, in each question. Often the questions would need to be broken down and these aspects asked separately. Whilst it is still important that children be included in research from a young age, the method from which their experience is elicited may need further development.

Parents and children were encouraged to not discuss their responses with each other whilst completing the questionnaires. When completing measures in clinic, children were not separated from their parents. This was decided as it may have increased anxiety for children, particularly young children, in a setting where this may have already been raised. Families also had the option to complete the questionnaires at home. Both scenarios may have meant that

parents and children were influenced in their responses by the presence of the other.

On the whole, families were approached to take part in the study whilst attending routine clinic appointments and a large proportion of families completed measures on site. It is possible that anxiety was raised for children and parents or that they were distracted by the thoughts about the appointment, both of which may have affected completion of the measures. In particular, if anxious, and some children were noticeably anxious about the blood tests that were due, this may have produced a negativity bias in reporting. For instance, questions that asked about worry about ITP symptoms may have received higher scores at this time.

As families were given the option to take the questionnaires away from clinic and return them by post, it is impossible to establish the exact amount of time passed between clinic appointment (and therefore most recent blood test) and questionnaire responses. Therefore measures of platelet count and questionnaire variables may relate to slightly different time points.

Access to interpreters meant that data from families who did not have a good comprehension of English could still be captured. However, due to time limitations available as families presented to clinic, completion of the full questionnaire packs was not possible. This included exclusion of the BRIEF measure which was the longest measure, with 86 items. Although, this

affected only three participants, this is an unfortunate methodological issue that meant that for these families this was not captured. There were some comments about particular items of the measures by those who spoke good English (meeting inclusion criteria) but to whom English was their second language. This included query over the terms 'cranky' and 'good attention span'. Providing synonyms of 'irritable' and 'how long they can concentrate' resolved these issues, although this deviated from the phrasing of the measure on these two occasions.

ITP is a changeable condition; platelet count often fluctuates within weeks or months. It is possible that psychological symptoms similarly vary across time. The questionnaires used asked parents and children to comment about different time periods- from one week (KIT measure) to six months (BRIEF). Firstly, this may have caused confusion for respondents or they may have neglected these different instructions. Furthermore, measures using a longer time frame may not have been sensitive enough to capture changes that might relate to fluctuating platelet count for instance. As Flores et al. commented (2014), children and parents may have been considering bleeding events further back in time than asked to comment on, or conversely focusing on the positive current situation but ignoring times of worse symptoms covered by the measures. Also, this study did not examine the effect of length of condition on child adjustment, and all results should be considered with this in mind. It is both useful to capture a long term

psychological profile of children with ITP, as well as recording of smaller changes over a short period using appropriately sensitive measures.

Clinicians, who provided severity ratings were not blind to the study objectives. This may have affected subjective ratings. However, the bleeding scale used (Provan et al., 2010) provided clear descriptors that should have guided clinicians to make objective ratings for this domain. Being aware of study objectives should not have had an impact on the scores that were provided from the clinical records.

Despite limitations, this study provides useful information about the psychological profile of children with ITP. Whilst some aspects of the condition may be similar to other conditions, some characteristics of the condition and its treatment, such as particular uncertainties around the illness, its visibility and its potential to restrict everyday life, may have a differential impact on children's adjustment. As the clinical understanding of ITP is still developing it is unclear whether biological or psychosocial processes can explain findings related to fatigue, executive functioning and emotional difficulties.

#### **4.10 Future research**

This study has begun to address gaps in the literature for the psychological profile for children with ITP and highlighted associations between different domains of adjustment. Although this research has highlighted potential

differences in psychological adjustment compared with the normal population it is unclear to what extent these issues are different from other chronic conditions. There is limited research on executive functioning and fatigue in different paediatric conditions. Future research should continue to use standardised measures to allow for comparisons across conditions.

If, through future research, there was further evidence to support executive functioning difficulties in children with ITP, studies could also examine the potential for biological cause to this. It is possible that undetected blood flow changes in the brain are having an impact. Alternatively, the disruption of platelets as carriers for various biological factors may have effects in the brain that are not, as yet, understood. For adults with ITP, it has been suggested that other bodily systems may be disrupted, which could have wide-ranging effects including cognitive deficits (Frith et al., 2011). Whilst the presentation of ITP in children is quite different to adults (Schulze, & Gaedicke, 2011), this hypothesis may remain true.

Given the discrepancies on some of the reports between parents and children, it is important that future studies take into account both self and informant reports of functioning. It is likely that there is no single objective 'truth' about symptoms but that both accounts provide useful information in to psychological characteristics.

Further research may want to explore the variables investigated in this study alongside other factors in the risk and resistance model (Wallander & Varni, 1992). Factors such as psychological well-being of parents, family background, psychological stress and functional ability may be areas for exploration, as well as the variables that may affect appraisal processes.

As this study found significant issues in emotional functioning for some children, this warrants further study. Studies may wish to use more detailed measures of emotional functioning that could differentiate anxiety and depression. A challenge for any study looking at the variables investigated here would be in differentiating the effects of each variable. This could be achieved in using different measures that have greater separation of items. Studies could use interventions to address particular symptoms (e.g., sleep hygiene, cognitive strategies, pharmacological or psychological treatment of mood difficulties) and observe the effect on other symptoms.

It is unclear whether appraisals examined in this study were a product of short-term evaluations or longer-term appraisal style. Longitudinal research may be able to provide information on this. For instance, whether appraisals vary related to symptoms and severity or whether some other factor alters appraisals. Related to this, it would be interesting to know whether appraisals changed over the course of the illness, including as the condition persisted for long enough to be categorised as a chronic condition. This may help to explain differences in quality of life ratings between those with persistent and

chronic ITP found in previous studies (Klaassen et al., 2013; Mokhtar, Farid, Shaker, & Farrag, 2014).

#### **4.11 Conclusions**

This study addressed gaps in the literature in relation to the psychological profile of child patients with ITP, specifically to establish that difficulties in fatigue, emotional-behavioural functioning, and executive functioning were elevated for some children in this group. Adjustment variables were significantly related to each other. This should be understood as both methodological and conceptual overlap. That is, emotional symptoms, fatigue and executive functioning present simultaneously and in relation to each other but also measures may include items that address more than one symptom. It remains a challenge for any research examining these variables to separate their unique and combined contributions. Disease characteristics were not generally associated with these adjustment outcomes. Several variables were related to quality of life, findings which have theoretical and clinical implications. Appraisal, as explored with a bespoke measure, was related to adjustment and quality of life. Understanding and integrating factors that contribute to good adjustment outcome in paediatric settings is a difficult task. This study furthers knowledge in the area of ITP but also the field of quality of life and adjustment in paediatric conditions more broadly.



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## Appendix 1: Strengths and Difficulties Questionnaire, Self-report (11 years +)

### Strengths and Difficulties Questionnaire

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of how things have been for you over the last six months.

Your Name .....

Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
I try to be nice to other people. I care about their feelings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am restless, I cannot stay still for long	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I get a lot of headaches, stomach-aches or sickness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I usually share with others (food, games, pens etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I get very angry and often lose my temper	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am usually on my own. I generally play alone or keep to myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I usually do as I am told	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I worry a lot	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am helpful if someone is hurt, upset or feeling ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am constantly fidgeting or squirming	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have one good friend or more	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I fight a lot. I can make other people do what I want	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am often unhappy, down-hearted or tearful	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other people my age generally like me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am easily distracted, I find it difficult to concentrate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am nervous in new situations. I easily lose confidence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am kind to younger children	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am often accused of lying or cheating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other children or young people pick on me or bully me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I often volunteer to help others (parents, teachers, children)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I think before I do things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I take things that are not mine from home, school or elsewhere	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I get on better with adults than with people my own age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have many fears, I am easily scared	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I finish the work I'm doing. My attention is good	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Your signature .....

Today's date .....

**Thank you very much for your help**

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*Appendix 2 Strengths and Difficulties Questionnaire, Parent report version*

**Strengths and Difficulties Questionnaire**

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's Name .....

Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Restless, overactive, cannot stay still for long	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often complains of headaches, stomach-aches or sickness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shares readily with other children (treats, toys, pencils etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often has temper tantrums or hot tempers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rather solitary, tends to play alone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Generally obedient, usually does what adults request	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Many worries, often seems worried	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Helpful if someone is hurt, upset or feeling ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Constantly fidgeting or squirming	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Has at least one good friend	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often fights with other children or bullies them	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often unhappy, down-hearted or tearful	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Generally liked by other children	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Easily distracted, concentration wanders	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nervous or clingy in new situations, easily loses confidence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kind to younger children	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often lies or cheats	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Picked on or bullied by other children	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often volunteers to help others (parents, teachers, other children)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thinks things out before acting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Steals from home, school or elsewhere	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gets on better with adults than with other children	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Many fears, easily scared	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sees tasks through to the end, good attention span	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Signature .....

Date .....

Parent/Teacher/Other (please specify:)

**Thank you very much for your help**

© Robert Goodman, 2005

PedsQL™ Multidimensional Fatigue Scale. Standard Version - English  
(UK)

**PARENT REPORT for TEENAGERS (ages 13-18)**

**DIRECTIONS**

Below is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

**0** if it is **never** a problem

**1** if it is **almost never** a problem

**2** if it is **sometimes** a problem

**3** if it is **often** a problem

**4** if it is **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

PedsQL 2

In the past **ONE month**, how much of a **problem** has this been for your child ...

<b>GENERAL FATIGUE (problems with...)</b>	Never	Almost Never	Sometimes	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

<b>SLEEP/REST FATIGUE (problems with...)</b>	Never	Almost Never	Sometimes	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

<b>MENTAL FATIGUE (problems with...)</b>	Never	Almost Never	Sometimes	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

## PedsQL™ Multidimensional Fatigue Scale

Standard Version - English (UK).

**TEEN REPORT (ages 13-18)**

### DIRECTIONS

Below is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

**0** if it is **never** a problem

**1** if it is **almost never** a problem

**2** if it is **sometimes** a problem

**3** if it is **often** a problem

**4** if it is **almost always** a problem

There are no right or wrong answers. If you do not understand a question, please ask for help.

PedsQL 2

In the past **ONE month**, how much of a **problem** has this been for you

GENERAL FATIGUE (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. I feel tired	0	1	2	3	4
2. I feel physically weak (not strong)	0	1	2	3	4
3. I feel too tired to do things that I like to do	0	1	2	3	4
4. I feel too tired to spend time with my friends	0	1	2	3	4
5. I have trouble finishing things	0	1	2	3	4
6. I have trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. I sleep a lot	0	1	2	3	4
2. It is hard for me to sleep through the night	0	1	2	3	4
3. I feel tired when I wake up in the morning	0	1	2	3	4
4. I rest a lot	0	1	2	3	4
5. I take a lot of naps	0	1	2	3	4
6. I spend a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4
6. I have trouble remembering more than one thing at a time	0	1	2	3	4



# PedsQL™

## Multidimensional Fatigue Scale

Standard Version - UK English

YOUNG CHILD REPORT (ages 5-7)

Instructions for interviewer:

*I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.*




Show the child the template and point to the responses as you read.

*If it is not at all a problem for you, point to the smiling face.*

*If it is sometimes a problem for you, point to the middle face.*

*If it is a problem for you a lot, point to the frowning face.*

*I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.*

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers?			

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

Appendix 5 PedsQL™ Multidimensional Fatigue Scale, young child report

PedsQL 2

**Think about how you have been feeling for the last few weeks. Please listen carefully to each sentence and tell me how much of a problem this is for you.**

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

<b>General Fatigue (PROBLEMS WITH...)</b>	<b>NOT AT ALL</b>	<b>SOME-TIMES</b>	<b>A LOT</b>
1. Do you feel tired?	0	2	4
2. Do you feel physically weak (not strong)?	0	2	4
3. Do you feel too tired to do things that you like to do?	0	2	4
4. Do you feel too tired to spend time with your friends?	0	2	4
5. Do you have trouble finishing things?	0	2	4
6. Do you have trouble starting things?	0	2	4

**Remember, tell me how much of a problem this has been for you for the last few weeks.**

<b>Sleep/Rest Fatigue (PROBLEMS WITH...)</b>	<b>NOT AT ALL</b>	<b>SOME-TIMES</b>	<b>A LOT</b>
1. Do you sleep a lot?	0	2	4
2. Is it hard for you to sleep through the night?	0	2	4
3. Do you feel tired when you wake up in the morning?	0	2	4
4. Do you rest a lot?	0	2	4
5. Do you take a lot of naps?	0	2	4
6. Do you spend a lot of time in bed?	0	2	4

<b>Cognitive Fatigue (PROBLEMS WITH...)</b>	<b>NOT AT ALL</b>	<b>SOME-TIMES</b>	<b>A LOT</b>
1. Is it hard for you to keep your attention on things?	0	2	4
2. Is it hard for you to remember what people tell you?	0	2	4
3. Is it hard for you to remember what you just heard?	0	2	4
4. Is it hard for you to think quickly?	0	2	4
5. Do you have trouble remembering what you were just thinking?	0	2	4
6. Do you have trouble remembering more than one thing at a time?	0	2	4

# How much of a problem is this for you?

Not at all



Sometimes



A lot



**Sample Copy- Do not use without permission**

## Appendix 6 Behaviour Rating Inventory of Executive Function (BRIEF)

Not included due to copyright restrictions

Appendix 7 . Kid's ITP Tools (KIT) – self report

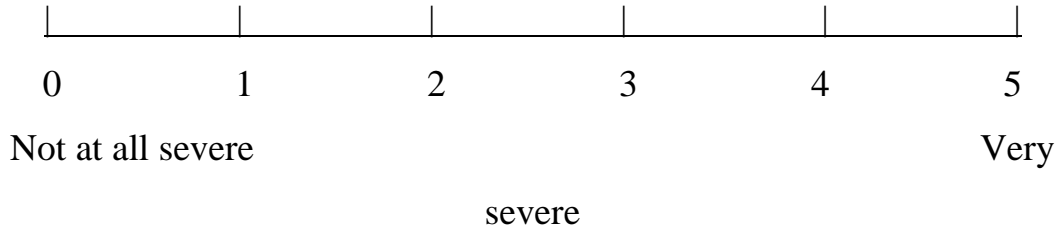
Not included due to copyright restrictions

## Appendix 8 Kid s ITP tool Parent proxy report

Not included due to copyright restrictions

Appendix 9 Visual Analogue Appraisal Scale for parents

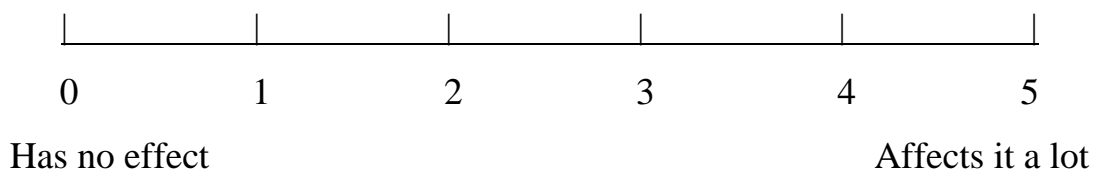
How severe would you rate your child's illness?



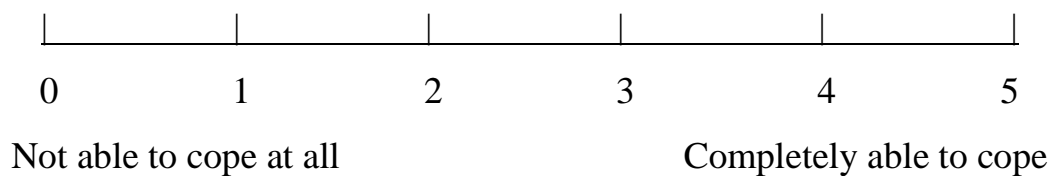
How much does your child's ITP affect *their* life?



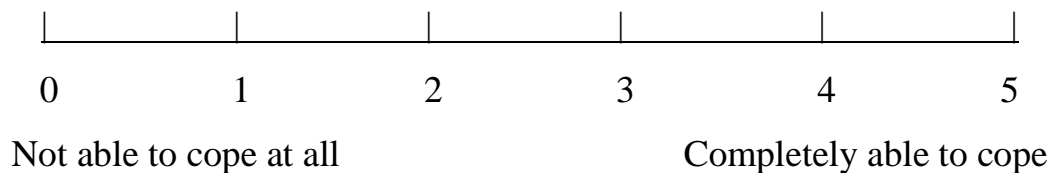
How much does your child's ITP affect *your* life?



How able do *you* feel to cope with your child's ITP?



How able do you feel *your child* is to cope with their ITP?



What part of your child's ITP bothers you the most?

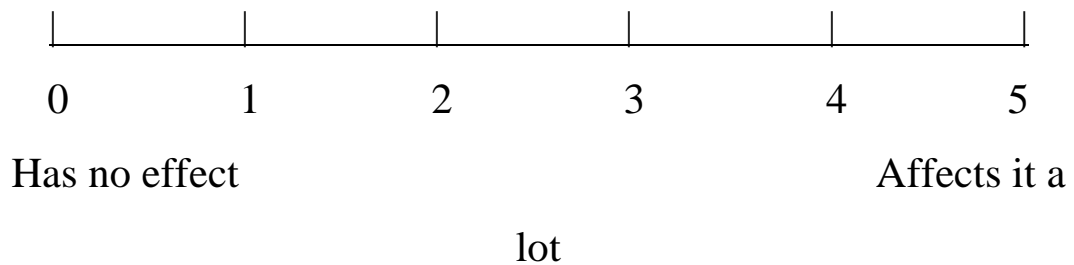
.....

Appendix 10 Visual Analogue Appraisal Scale for children aged 7-16

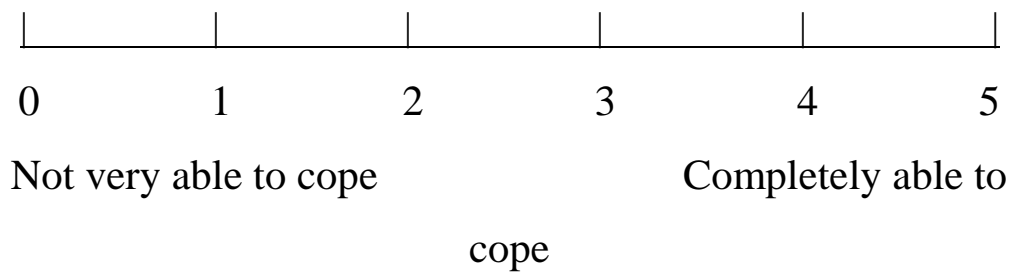
How bad/severe is your illness?



How much does ITP affect your life?



How able do you feel to cope with your ITP?



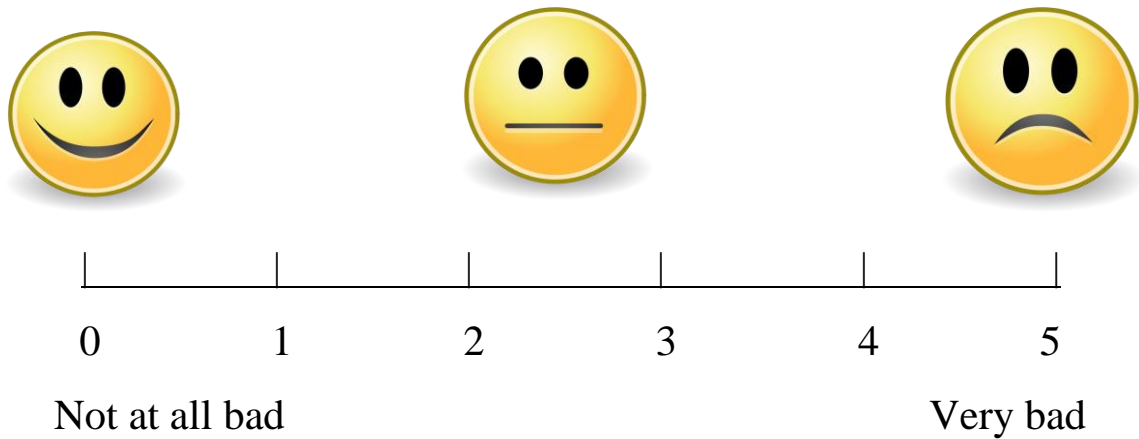
What part of your ITP bothers you the most?

.....

Visual Analogue Scale- Child version 7-16 years



How bad is your illness?



What part of your illness worries/bothers you the most?

.....



# Child ITP study

- Are you a young person with ITP?
  - Do you have a child with ITP?

We are doing some research at [removed]  
Hospital in to Immune Thrombocytopenia (ITP)  
in children

The main areas we are looking at are fatigue,  
concentration and behaviour and how these affect  
well-being.

Parents and children would be asked to fill in  
some questionnaires about these areas.

If you are interested in taking part in this research  
or would like more information, please speak with  
**your clinician** or contact [removed], Trainee  
Clinical Psychologist/Chief Investigator on  
[removed]

### **Participant Information sheet**

#### **Project: The thoughts, feelings and behaviours of children with Immune Thrombocytopenia (ITP)**

We would like to invite you and your child to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve. One of our team will go through the information sheet with you and answer any questions you have. We'd suggest this should take about 10 minutes.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear.

#### **Part 1**

##### **Why is the study being done?**

We believe it will aid research in the important area of ITP in children. We hope the findings will help us to better understand the factors that influence well-being for children with ITP. This will enable us to provide better care and support for families with children with ITP.

##### **Why are we being invited to take part in the research?**

You and your child are being asked to take part as your child has ITP. We are hoping about 50-75 families in total will participate, recruited from NHS hospitals.

##### **Do I have to take part?**

It is up to you to decide to join the study. You or your child are free to withdraw at any time, without giving a reason. This would not affect the standard of care your child receives. You can choose to participate if your child does not participate. Similarly, your child can complete the questions if you do not wish to participate.

##### **What will happen if we take part?**

Children who take part in this study will be asked to complete some questions about their condition and how it affects them. The amount of questions will depend on the age of the child, taking up to maximum of 20 minutes. These will be about how they feel and behave, their fatigue/tiredness and some questions about what it's like to have ITP.

As parents/carers you will also be asked to fill in some questionnaires about your child. You will be asked about your child's feelings and behaviours, their fatigue/tiredness and what it's like for them to have ITP. You will also be asked about their thinking skills. This should take up to a maximum of 30 minutes.

You can complete these at the same time as your routine clinic appointment and hand them straight back to us. Alternatively, we can give you an envelope to post them back to us. Some details from your child's clinical notes will be provided by your clinician. These will be length of time since of diagnosis, bleeding severity, platelet count, the type and amount of treatment received and any reaction to it. No additional clinical tests will need to be completed. We will follow ethical and legal practice and all information about you will be handled in confidence. The details of this are included in Part 2.

## Appendix 14 Parent information sheet

### **Are there any disadvantages of taking part?**

We do not anticipate any distress to arise during the completion of these questionnaires. However, if you or your child experience any distress you are advised to speak to the main researcher (removed) in the first instance. You or your child can stop completing the questionnaires at any time. You could also be referred to the Psychology department if necessary. The study may not have direct benefit to you, but the information we get will help improve the treatment and support for other children with ITP.

### **Part 2**

#### **Will my information stay confidential?**

Storage of all material will adhere to the Caldicott Principles, and in line with the Data Protection Act (1998). This means the data will be kept only as long as is needed for the purposes of research and its audit, typically a maximum of 5 years following publication. All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be identified. Only members of research team will be allowed to see the raw data of the study. The only time information would be shared outside of this would be if you or your child told us something that suggested someone was at risk of serious harm. If this happened, we may need to involve other professionals. We would try to discuss this with you before doing so.

#### **What will happen to the results?**

The results of the study may be published. Any results published would not contain your name or any information that identifies you or your child.

Once the research is completed, we will produce a summary of the results for participants. Please let us know now if you would like a copy of this. Alternatively, you will be able to ask your clinician for this.

#### **Who has reviewed the research?**

This study has been reviewed and approved by an independent group of people, called a Research Ethics Committee, and by the Psychology Department internal ethical procedure at Royal Holloway, University of London. [removed] have also given permission for this study to be carried out. The members of the research team have been checked and cleared by the Disclosure and Barring Service (previously the Criminal Records Bureau).

#### **What happens next?**

If you are happy to take part in the research, please complete the consent form overleaf to indicate whether you agree to take part and whether you agree for your child to take part in this study. Please retain this sheet for your future information.

Thank you for taking the time to read this information.

[removed]  
Trainee Clinical Psychologist/ Chief Researcher  
[removed]

[removed]  
Principal Researcher  
[removed]

## Appendix 14 Parent information sheet

For more information and support around ITP, you can contact the ITP Support Association: [www.itpsupport.org.uk](http://www.itpsupport.org.uk), Tel: 0844 7770 559

If you would like to discuss with someone whether or not you should participate in research generally please contact the Patient Advice and Liaison Service (PALS) on [removed].

If you have any **comments or concerns** during the study you may discuss these with the researcher who will do their best to answer your questions. If you wish to go further and complain about any aspect of the way you have been approached or treated during the study, you can do this through the NHS Complaints Procedure. Details for this are available through your clinic.

Your signed consent form will be stored separately from the responses you provide

NB: You may retain this information sheet for reference and contact us with any queries

***What is it like to have ITP?***

Hello. We are asking if you would join a research project about ITP. Before you decide if you want to join in, it's important to understand why the research is being done and what it will involve for you. So please read this leaflet carefully. Talk to your family, doctor or nurse if you want to and ask me any questions.

**What is the research about?**

I am interested in finding out about what it's like to have ITP, and how this affects how you feel. This is important to help us understand the experience of young people with ITP better and offer support at the right times.

**Why have I been invited?**

You have been invited because you have ITP and between the age of 5 and 16 years old.

**Do I have to take part?**

No. If you don't want to take part that's OK. Your decision to take part or not will not affect any of the treatment you receive. If you do take part, it's also OK for you to decide to stop doing the research at any time or choose not to answer a particular question. You don't even have to say why. As you are under 16 years old your parent or carer will also agree for you to join in this project.

**What would I have to do?**

If you decide to take part, you will be given some questionnaires to complete. These will be about how tired you are, how you feel and what it's like to have ITP. These should take up to 20 minutes. You can fill them in whilst you are at the clinic or you can take them home and we can give you an envelope to send them back to us. Your parent or carer will also be asked to complete some questions but they can say no to this if they wish.

**What will happen to the information I give you?**

We will keep your information private and confidential- the answers you give will be collected and only looked at by members of the research team. The questionnaires will not have your name on and so your answers will not be able to be linked to you.

The only time I would have to tell someone about what had been written or said was if you (or your parent/carer) said something that makes us worried that someone may be at risk. Then we may need to talk to someone else about this. We would let you know if we needed to do this.

**What are the possible benefits of taking part?**

I can't promise that this study will help you directly but the results will help to improve future care for young people living with ITP. You can ask to be sent a summary report of what we found out from the study once the study has been completed.

**Could anything bad happen if I take part?**

The study has been checked by a group of people called a Research Ethics Committee who have decided that this research is fair and safe.

We don't expect you will have any problems taking part- we just want to hear about your views! But if you are not happy about anything you can tell me or talk to your doctor or nurse, or your parents/carers. You have the choice to leave the study at any time if you want to.

Thank you for taking time to read about this study.

**So if I do want to take part, what should I do now?**

If you decide that you want to take part, that's great. As you are under 16 years old, you **and** your parent/guardian will need to sign the consent forms attached.

**If you have any further questions or comments, you can ask your parents or doctor for my contact details**

**For more information and support around ITP, see the ITP Support Association: [www.itpsupport.org.uk](http://www.itpsupport.org.uk)**

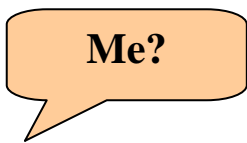


**Project for children with problems with their blood**  
**- what is it like?**



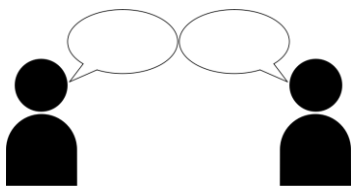
My name is Sarah. I am learning to be a psychologist.

We want to find out more about what it's like to have problems with your blood.



You are being asked to take part in this project because you have something wrong with your blood.

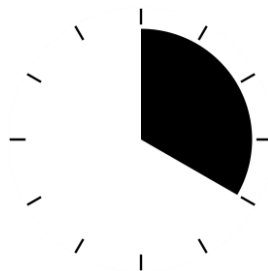
You can choose if you want to take part or not.



If you want to take part, you will either be asked some questions or you will write things down about what it's like to have problems with your blood.



This will take up to 20 minutes.



What you write or say will be kept private.

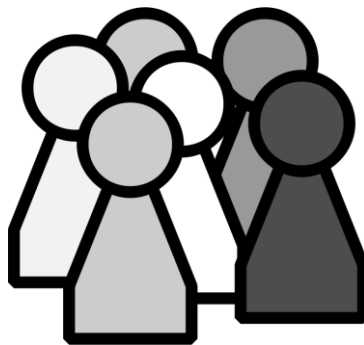


You can stop at any time. You can choose not to answer a question



If you are upset about anything in the questions, you can tell your parent, doctor or me.

We cannot promise the study will help you but the information we get might help other children who have problems with their blood.



Do you have any questions?



Appendix 17 Child assent form

**ASSENT FORM FOR CHILDREN AND YOUNG PEOPLE**

**Project title : Problems with your blood- what is it like? / How do young people feel who have ITP?**

Young person/child (or if unable, parent on their behalf) to circle all they agree with:

Have you read about this project or has

somebody else explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/No

Have you had your questions

answered in a way you understand? Yes/No

Do you understand it's OK to stop taking part at any time? Yes/No

Do you understand your information

will be kept safe and private? Yes/No

Are you happy to take part? Yes/No

If any answers are "no" or you don't want to take part, don't sign your name!

If you do want to take part, you can write your name below

Your name

Date

The person who explained this project to you needs to sign too:

Print Name

Sign

Date

Thank you for your help.



Appendix 18 Consent form for 16 year olds

**Consent form for young people, 16 years and over**

Title of project: **The thoughts, feelings and behaviours of children with ITP**

Name of Chief investigator: **[removed]**

- |  |  |
|--|--|
| 1. I confirm that I have read and understood the young person information sheet dated 01/07/2014 (version 2) for the above study and have had the opportunity to ask questions.  |  |
| 2. I confirm that I have had sufficient time to consider whether or not I want to participate in the study   |  |
| 3. 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   |  |
| 4. I understand that selected/relevant details from my medical notes will be used in this study.   |  |
| 5. I understand that my data will be anonymised and identifying information removed.   |  |
| 6. I understand that relevant data collected during the study may be looked at by individuals 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 this data. |  |

NB. Your signed consent form will be stored separately from the responses you provide

I have read the above and I agree to participate in the above study.  
(please tick above boxes and sign below)

_____	_____	_____
Name (please print)	Date	Signature
_____	_____	_____
Researcher (to be contacted if there are any problems)	Date	Signature



Appendix 20 Demographics form

Please do not put your name or your child's name anywhere in this booklet

Please complete the following:

Your age \_\_\_\_\_

Your gender M  F

Age of your child \_\_\_\_\_

Gender of your child M  F

Your relationship to child (e.g. parent): \_\_\_\_\_

Your ethnicity (please tick):

- |   |  |
|---|--|
| <input type="checkbox"/> White British          | <input type="checkbox"/> Black Caribbean and White |
| <input type="checkbox"/> Other White background | <input type="checkbox"/> Black African and White   |
| <input type="checkbox"/> Black British          | <input type="checkbox"/> Asian and White           |
| <input type="checkbox"/> Black African          | <input type="checkbox"/> Other Dual Heritage       |
| <input type="checkbox"/> Black Caribbean        | <input type="checkbox"/> Chinese                   |
| <input type="checkbox"/> Other Black background | <input type="checkbox"/> Traveller                 |
| <input type="checkbox"/> Indian                 | <input type="checkbox"/> Other Ethnic Group        |
| <input type="checkbox"/> Pakistani              | <input type="checkbox"/> Prefer not to say         |
| <input type="checkbox"/> Bangladeshi            |  |
| <input type="checkbox"/> Other Asian background |  |

Ethnicity of child (please specify if different) \_\_\_\_\_

or  same ethnicity

*Memorandum*

**To:** [removed]  
**From:** [removed] (on behalf of the Research Sub-Committee and Course Executive)  
**Date:** 13<sup>th</sup> February 2014  
**Copy To:** [removed]  
**Re:** Main Research Project Proposal

---

The Research Sub-Committee has considered your Main Research Project Proposal response and has decided to give you **Approval**. Your research costs have also been approved. Please note that if these costs change and you do not re-submit an amended form for approval prior to incurring any additional costs, these additional costs will not be reimbursed.

Appendix 22 Clinical site Research committee approval

[removed]  
Psychosocial Services  
[removed]

13<sup>th</sup> June 2014

Dear [removed]

**Title:       The Cognitive,  
              Behavioural and  
              Psychological Profile  
              of Children with ITP  
              and Factors  
              Influencing their  
              Wellbeing**

R&D Ref:     14HT02

Funding:     Clinical Own Account Decision:     Scientific Approval

I am writing to inform you that the [Research Committee] reviewed your application and has no objections to the conduct of this project at [removed].

The Committee has some comments on the Project, which are in preparation and I shall send these on to you shortly. In the meantime, I thought it best to inform you of the Committee's approval and wish you well with your Ethics application.

You will shortly receive a checklist of documents that are required for R&D approval. Once all the documents have been received you will receive an R&D approval email and you can commence your project.

Kind Regards

Professor [removed]  
Chair  
[Research Committee]



## Appendix 23 Comments from main clinical site Research Committee

[removed]  
Psychosocial Services  
[removed]

10<sup>th</sup> July 2014

Dear [removed]

Title: The Cognitive, Behavioural and Psychological Profile of Children with Immune Thrombocytopenia Purpura (ITP) and Factors Influencing their Wellbeing

R&D Ref: 14HT02  
Funding: Clinical Own Account  
Decision: Scientific Approval

Further to the Scientific Approval letter that I sent you on 13th June 2014 I am writing to let you have the comments from the [Research committee] member who presented your project to the committee on 10th June 2014. I hope that you find these comments helpful.

### **[removed] 18month DClin study from Royal Holloway.**

Study looking at the effects of ITP on children and their families. Treatment just based on platelet count, bleeding. Aim to look at common secondary characteristics (fatigue, difficulties with concentration impacting academic performance and behaviour problems, impact on well-being and qofL) and determine if these should be factored into treatment decision. Also known that cognitive appraisal impact on adjustment to a chronic illness and this will be evaluated.

**Cohort/Inclusions/exclusions** Main group is parents and children” if there is enough of them”. 49-66 participants required based on power calculation from 75 patients seen/year. If not sufficient are considering approaching other centres. We advised to do this early on given issues of time taken with local research approvals particularly as they need high opt in in order to have sufficient power.

Also plan to exclude those who do not have a “reasonable” command of English or if they have a disability. Would be appropriate to define “reasonable” (eg not requiring an interpreter) and “disability” needs to be expanded eg. learning, communication, hearing impairment etc

**Methods:** How are the features of fatigue and concentration likely to affect questionnaire completion?

*Appendix 23 Comments from main clinical site Research Committee*

Some concerns as to how data collection will be completed by the parent and child in the same session if the parent needs to help the child. Needs to be clear which are completed on own, with researcher, with parent. Says researcher will conduct the questionnaires with the young children. How will they engage young children to do this? Will parent need to help the younger children? Will the researcher need to ensure only so many patients per clinic? Would be helpful to pilot the process not just for time taken but logistics.

Advised optimum would be for all the parent questionnaires to be completed in the same context ie clinic. Is it possible that forms completed at home could be completed differently, and there is the risk that these would not be completed and returned.

**Analysis** It is unclear how the VAS cognitive appraisal measures will be analysed; they are not part of either hypothesis. ITP categories needed as there are degrees of severity. Suggested mild, moderate, severe and should be based on previous literature.

**Other comments:** Needs a GAANT chart and signatures on the form, suggest the cohort is called Children and Young People, the written information sheets will need to be adjusted for the age group. The PPI is good.

I just need to remind you that neither this letter nor the previous one constitute R&D approval and that you may not start your project till the Research Governance department has issued you with a formal R&D approval letter.

Kind Regards

Professor [removed]  
Chair  
[Research Committee]



## **Health Research Authority**

**National Research Ethics Service**

[removed]

04 August 2014 [removed]

Royal Holloway, University of London Egham

Surrey TW20 0EX

Dear [removed]

<b>Study title:</b>	<b>The cognitive, behavioural and psychological profile of children with ITP</b>
<b>REC reference:</b>	<b>14/NW/1172</b>
<b>IRAS project ID:</b>	<b>146242</b>

The Proportionate Review Sub-committee of the NRES Committee North West - Greater Manchester West reviewed the above application on 01 August 2014.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so.

Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager [removed], [removed]

### **Ethical opinion**

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

### **Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

## *Appendix 24 NHS NRES Ethics Favourable opinion with conditions*

1. The Committee would like the Participant Information for 5-10 year olds revised to change the clock to say 20 minutes not 25 minutes.
2. The Committee would the footer on the parents information sheet amended, this is not a consent form.
3. The Committee would like the fields over all the dates on documents removed and replaced with a fixed date which should match the dates submitted on the checklist.

**You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.**

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission (“R&D approval”) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

*Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.*

*Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations.*

Registration of Clinical Trials

## *Appendix 24 NHS NRES Ethics Favourable opinion with conditions*

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett ([catherineblewett@nhs.net](mailto:catherineblewett@nhs.net)), the HRA does not, however, expect exceptions to be made.

Guidance on where to register is provided within IRAS.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion”).

## **Summary of discussion at the meeting**

### **Informed consent process and the adequacy and completeness of participant information**

The Committee requested the changes as noted in the favourable opinion with conditions.

## Appendix 24 NHS NRES Ethics Favourable opinion with conditions

### Approved documents

The documents reviewed and approved were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [Recruitment poster]	1	01 July 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity Cover letter]	1	02 September 2013
IRAS Checklist XML [Checklist_17072014]		17 July 2014
Letter from statistician [Statistician comments]	1	16 April 2014
Non-validated questionnaire [Parent Visual Analogue Scale]	1	01 July 2014
Non-validated questionnaire [7-16 Visual Analogue Scale]	1	01 July 2014
Non-validated questionnaire [5-7 Visual Analogue Scale]	1	01 July 2014
Participant consent form [Child assent form]	1	01 July 2014
Participant consent form [Parent consent form]	1	01 July 2014
Participant consent form [16 YP]	1	23 July 2014
Participant information sheet (PIS) [Young child Info sheet]	1	01 July 2014
Participant information sheet (PIS) [Parent info sheet]	1	01 July 2014
Participant information sheet (PIS) [11-16 child Info sheet]	1	01 July 2014
REC Application Form [REC_Form_17072014]		17 July 2014
Research protocol or project proposal [Major Project Proposal]	3	01 July 2014
Summary CV for Chief Investigator (CI) [████████.CV]	1	01 April 2014
Summary CV for student [Student CV]	1	01 April 2014
Summary CV for supervisor (student research) [Academic Supervisor CV]	1	20 February 2014
Validated questionnaire [KIT measure child]	UK v.1	01 August 2007
Validated questionnaire [Kit measure Parent]	Uk v. 1	01 August 2007
Validated questionnaire [PedsQL Fatigue]		
Validated questionnaire [SDQ child]		
Validated questionnaire [SDQ parent]		

### Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

## After ethical review

### Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
  - Progress and safety reports
  - Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

### Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee’s best wishes for the success of this project.

**14/NW/1172**

**Please quote this number on all correspondence**

Yours sincerely

[removed]

(Research committee) Chair

Email: [removed]

Appendix 24 NHS NRES Ethics Favourable opinion with conditions

*Enclosures: List of names and professions of members who took part in the review*

*Copy to: [removed]  
[removed]*

**Attendance at PRS Sub-Committee of  
the REC meeting on 01 August 2014**

**Committee Members:**

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
[removed]	Consultant in Communicable Diseases	Yes	
[removed]	Lay Member	Yes	
[removed]	Consultant in Public Health Medicine	Yes	

**Also in attendance:**

<i>Name</i>	<i>Position (or reason for attending)</i>
[removed]	REC Manager





## Health Research Authority

National Research Ethics Service

[removed]

11 August 2014 [removed]  
 Royal Holloway, University of London Egham  
 Surrey TW20 0EX

Dear [removed]

**Study title:** The cognitive, behavioural and psychological profile of children with ITP and factors influencing

**REC reference:** 14/NW/1172

**IRAS project ID:** 146242

Thank you for your email of 5 August 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 04 August 2014

### Documents received

The documents received were as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Participant consent form [16 Years and Above]	2	23 July 2014
Participant consent form [Assent Form]	2	01 July 2014
Participant consent form [Parent]	2	01 July 2014
Participant information sheet (PIS) [Parents]	2	01 July 2014
Participant information sheet (PIS) [5-10 Years Olds]	2	01 July 2014
Participant information sheet (PIS) [11-16 Year Olds]	2	01 July 2014

### Approved documents

The final list of approved documentation for the study is therefore as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [Recruitment poster]	1	01 July 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity Cover letter]	1	02 September 2013
IRAS Checklist XML [Checklist_17072014]		17 July 2014
Letter from statistician [Statistician comments]	1	16 April 2014

Non-validated questionnaire [7-16 Visual Analogue Scale]	1	01 July 2014
Non-validated questionnaire [Parent Visual Analogue Scale]	1	01 July 2014
Non-validated questionnaire [5-7 Visual Analogue Scale]	1	01 July 2014
Participant consent form [16 Years and Above]	2	23 July 2014
Participant consent form [Parent]	2	01 July 2014
Participant consent form [Assent Form]	2	01 July 2014
Participant information sheet (PIS) [Parents]	2	01 July 2014
Participant information sheet (PIS) [11-16 Year Olds]	2	01 July 2014
Participant information sheet (PIS) [5-10 Years Olds]	2	01 July 2014
REC Application Form [REC_Form_17072014]		17 July 2014
Research protocol or project proposal [Major Project Proposal]	3	01 July 2014
Summary CV for Chief Investigator (CI) [████████ CV]	1	01 April 2014
Summary CV for student [Student CV]	1	01 April 2014
Summary CV for supervisor (student research) [Academic Supervisor CV]	1	20 February 2014
Validated questionnaire [PedsQL Fatigue]		
Validated questionnaire [Kit measure Parent]	Uk Version 1	01 August 2007
Validated questionnaire [SDQ child]		
Validated questionnaire [KIT measure child]	UK Version 1	01 August 2007
Validated questionnaire [SDQ parent]		

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

**14/NW/1172**

**Please quote this number on all**

Yours sincerely

[removed]  
REC Manager

E-mail: [removed]

Copy to: [removed]  
[removed]

*Appendix 26 Research and Development Approval*

[removed]

15/08/2014

[removed]

Dear [removed],

Project Title : The cognitive, behavioural and psychological profile of children with ITP and factors influencing their well-being

Protocol version	3
Protocol date	1st July 2014
REC Reference	14/NW/1172
R&D Reference	14HT02
Sponsor	Royal Holloway University of London [removed]

Notification of [removed] Hospital NHS Permission.

The research approval process for the above named study has been completed successfully. I am pleased to issue approval, on behalf of [removed] for the above study to proceed.

All research carried out within this Trust must be in accordance with the principles set out in the Research Governance Framework for Health and Social Care (April 2005, 2nd edition, Department of Health (DH)).

This approval is issued on the basis of the project documentation submitted to date. The approval may be invalidated in the event that the terms and conditions of any research contract or agreement change significantly and while the new contract/agreement is negotiated.

The conditions for host site approval are as follows:

- [removed] must have appropriate contractual arrangements in place with [removed] to participate in this research study.
- The Principal Investigator {PI} must ensure compliance with protocol and advise the Joint R&D Office of any change(s) to the protocol. Failure of notification may affect host approval status.

## Appendix 26 Research and Development Approval

- Under the terms of the Research Governance Framework (RGF), the PI is obliged to report any Serious Adverse Events (SAEs) to the Sponsor and the Joint R&D Office in line with the study protocol and Sponsor requirements. Adverse Incidents (AEs) must also be reported in accordance with the Trust Adverse Incident Reporting Policy & Procedures.
- The PI must ensure appropriate procedures are in place to action urgent safety measures.
- The PI is responsible for the set up and maintenance of the Investigator Site File (ISF) generated to store all documentation relating to this project.
- The PI must ensure that all named staff are compliant with the Data Protection Act (DPA) 1998, Human Tissue Act (HTA) Mental Capacity Act (MCA) 2005 and all other applicable statutory guidance and legislation.
- The PI must allow monitoring and auditing by the Sponsor and the Joint R&D Office.
- The PI must report any cases of suspected research misconduct and fraud to the Joint R&D Office.
- The PI must provide an annual report to the Joint R&D Office for all research involving NHS patients, staff and/or resources. The PI must notify the Joint R&D Office of any presentations of such research at scientific or professional meetings, or on the event of papers being published and any direct or indirect impacts on patient care.

Failure to comply with the above conditions and regulations will result in the suspension of the research project.

Please contact the Joint R&D Office if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Yours sincerely,

[removed]

*Research Management  
and Governance Officer  
Joint Research and  
Development Office*

## Appendix 27 Results Summary for participants

### **ITP project- results summary**

We investigated several areas of well-being for children with ITP that have not been looked at in previous research.

We asked children and their parents about behaviour, tiredness, thinking skills, and what it's like to have ITP.

We found that:

- Children with ITP have more problems with tiredness than children without ITP
- Some children with ITP have problems with feeling sad or worried at times, and this was more so than another group of children without ITP
- Some children with ITP have difficulties with 'thinking skills' which we call 'executive functioning'. These are a particular set of thinking skills concerned with planning and organising, initiation, and self-regulation.
- Generally, platelet count was not associated with tiredness, thinking skills or well-being
- Parents rated their child's ITP as worse than children themselves did, and also worse than clinicians felt it was.
- Children with lower bleeding severities felt more able to cope with the condition
- Findings indicated that subjective ratings of the illness may have been more important than objective ratings (ie. platelet count)

Parents and children commented that what they were particularly worried about were visual signs of ITP, the uncertainty about the condition, the restriction on activities and blood tests.

The above results are based on the average scores for all children that took part. However, on all measures, the majority of children were not having significant difficulties and were managing well despite their ITP.

These are similar findings as found in other children with physical health conditions. More research is needed to help us know what results in better outcome for some children and not others. These findings help us develop care and support for children and families with experience of ITP.

If you have any further questions or comments, please contact [removed], Chief Researcher, by email, [removed]