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Impact of fatigue and reduced HRQoL

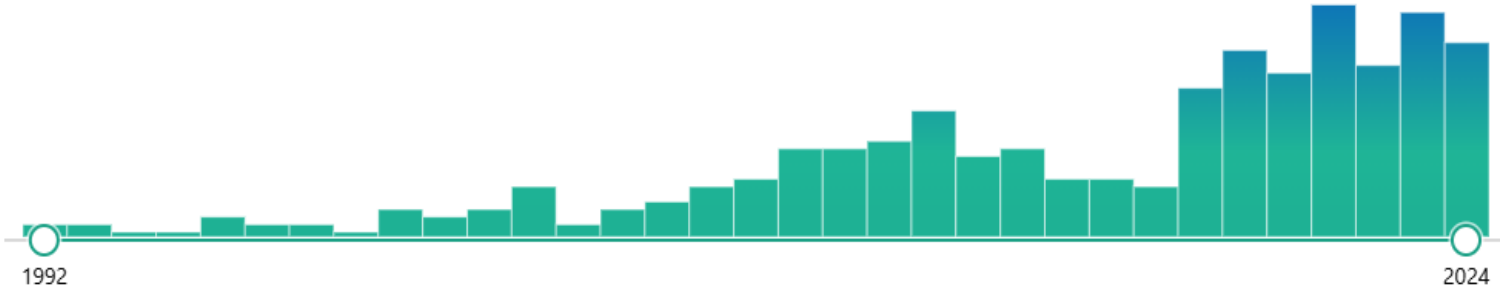
Disclosures of Henrik Frederiksen

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	X						
Sanofi	X					X	
Grifols							X
Alexion	X						
Johnson & Johnson							X

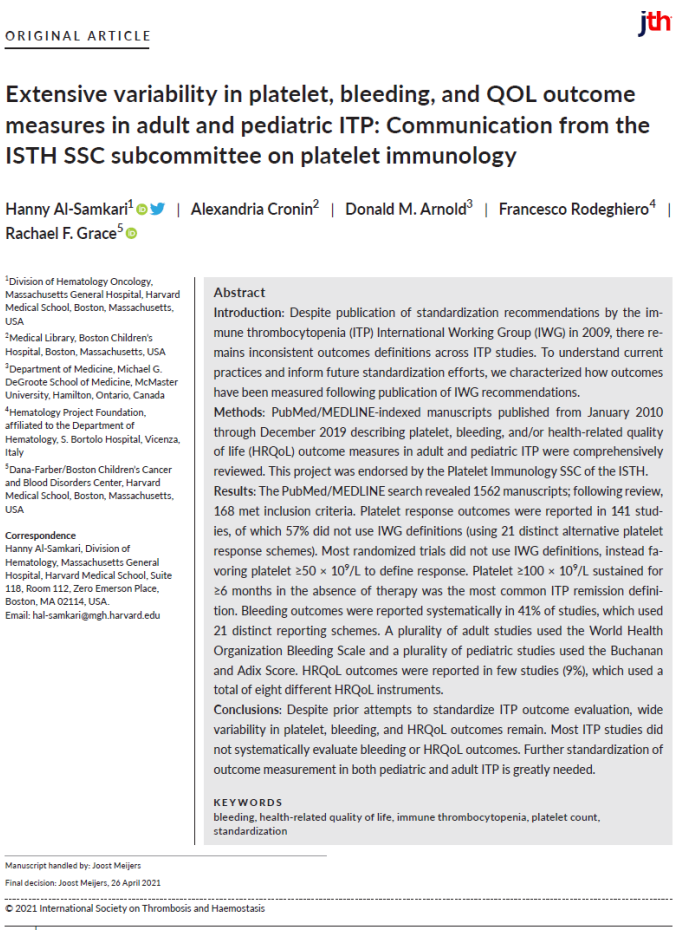
The largest unmet need in patients with ITP..

HRQoL and Fatigue in ITP on the rise??

268 hits on ”ITP” AND ”Health related quality of life”



Additional 57 hits on ”ITP” AND ”Fatigue”



ORIGINAL ARTICLE

jth

Extensive variability in platelet, bleeding, and QOL outcome measures in adult and pediatric ITP: Communication from the ISTH SSC subcommittee on platelet immunology

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Abstract

Introduction: Despite publication of standardization recommendations by the immune thrombocytopenia (ITP) International Working Group (IWG) in 2009, there remains inconsistent outcomes definitions across ITP studies. To understand current practices and inform future standardization efforts, we characterized how outcomes have been measured following publication of IWG recommendations.

Methods: PubMed/MEDLINE-indexed manuscripts published from January 2010 through December 2019 describing platelet, bleeding, and/or health-related quality of life (HRQoL) outcome measures in adult and pediatric ITP were comprehensively reviewed. This project was endorsed by the Platelet Immunology SSC of the ISTH.

Results: The PubMed/MEDLINE search revealed 1562 manuscripts; following review, 168 met inclusion criteria. Platelet response outcomes were reported in 141 studies, of which 57% did not use IWG definitions (using 21 distinct alternative platelet response schemes). Most randomized trials did not use IWG definitions, instead favoring platelet ≥50 × 10^9/L to define response. Platelet ≥100 × 10^9/L sustained for ≥6 months in the absence of therapy was the most common ITP remission definition. Bleeding outcomes were reported systematically in 41% of studies, which used 21 distinct reporting schemes. A plurality of adult studies used the World Health Organization Bleeding Scale and a plurality of pediatric studies used the Buchanan and Adix Score. HRQoL outcomes were reported in few studies (9%), which used a total of eight different HRQoL instruments.

Conclusions: Despite prior attempts to standardize ITP outcome evaluation, wide variability in platelet, bleeding, and HRQoL outcomes remain. Most ITP studies did not systematically evaluate bleeding or HRQoL outcomes. Further standardization of outcome measurement in both pediatric and adult ITP is greatly needed.

KEYWORDS
bleeding, health-related quality of life, immune thrombocytopenia, platelet count, standardization

Manuscript handled by: Joost Meijers
Final decision: Joost Meijers, 26 April 2021

Terminology is changing

ITP is .....

*..an autoimmune platelet disorder ....with **bleeding, fatigue, and reduced health-related quality of life ..***

Al-Samkari *et al.*, JTH 2021; 19: 2348-54

HRQoL outcomes in -

ITP Studies 2010-19

- Systematic review of outcomes in 168 ITP studies
  - 84% platelet response
  - 40% bleeding
  - **9% HRQoL**

ITP guidelines

	ASH 2019	Int. consensus report 2019	German guidelines 2023
HRQol mentions	2	10	14
Section devoted to HRQoL	-	+	++
Focus on HRQoL in treatment and outcomes	+	++	++
Discuss different HRQoL measures	-	+	-

Al-Samkari *et al*., J Thromb Hemostas 2021; 19: 2348-54, Neunert C *et al. Blood Adv* 2019; 3: 3829-66, Provan D *et al*. *Blood Adv* 2019; 3: 3780-3817
Matzdorff A *et al. Oncol Res Treat* 2023; 46: 5-44

ITP – World Impact Survey (I-WISh)

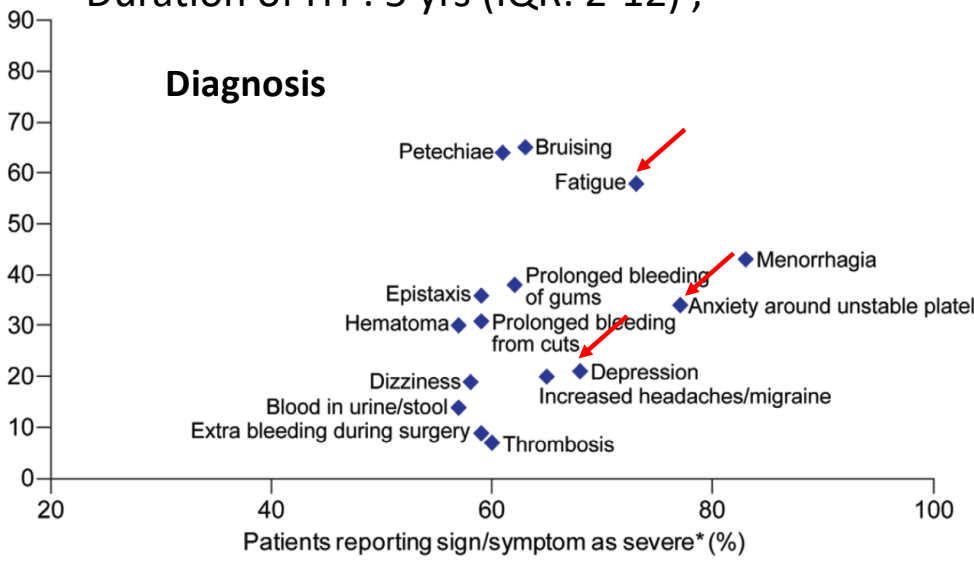
- 1507 pts from 13 countries
- Recruitment -
  - Patient association groups (57%)
- Symptoms and HRQoL assessed at -
  - Diagnosis (retrospectively)
  - Survey completion
- Duration of ITP: 5 yrs (IQR: 2-12) ,

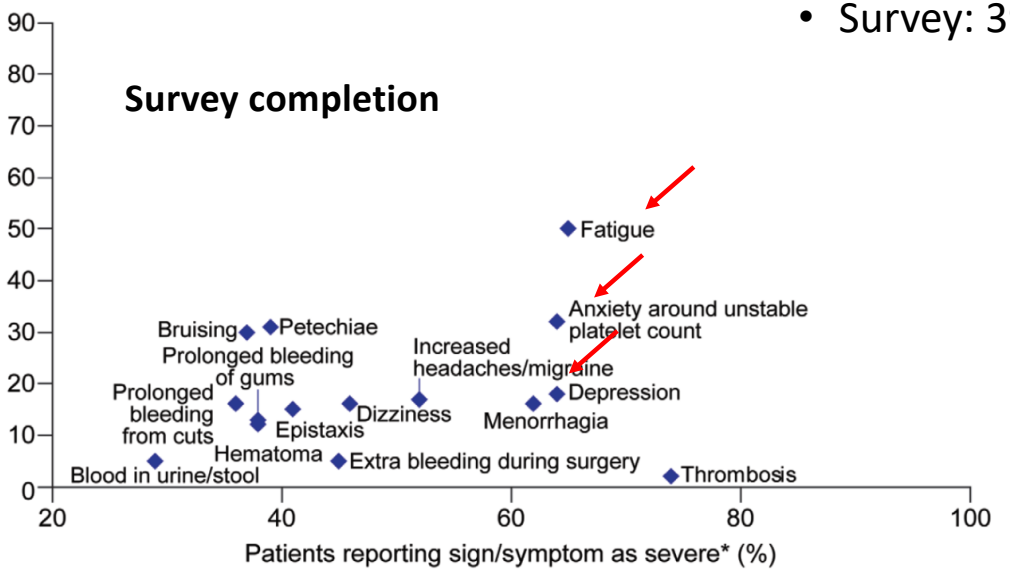
<u>Demographics</u>

- Mean age: 47 yrs
- Women: 65%
- Median duration of ITP: 5 yrs (IQR: 2-12)
- Splenectomized: 20%

<u>High or very high symptom burden</u>

- Diagnosis: 48%
- Survey: 39%





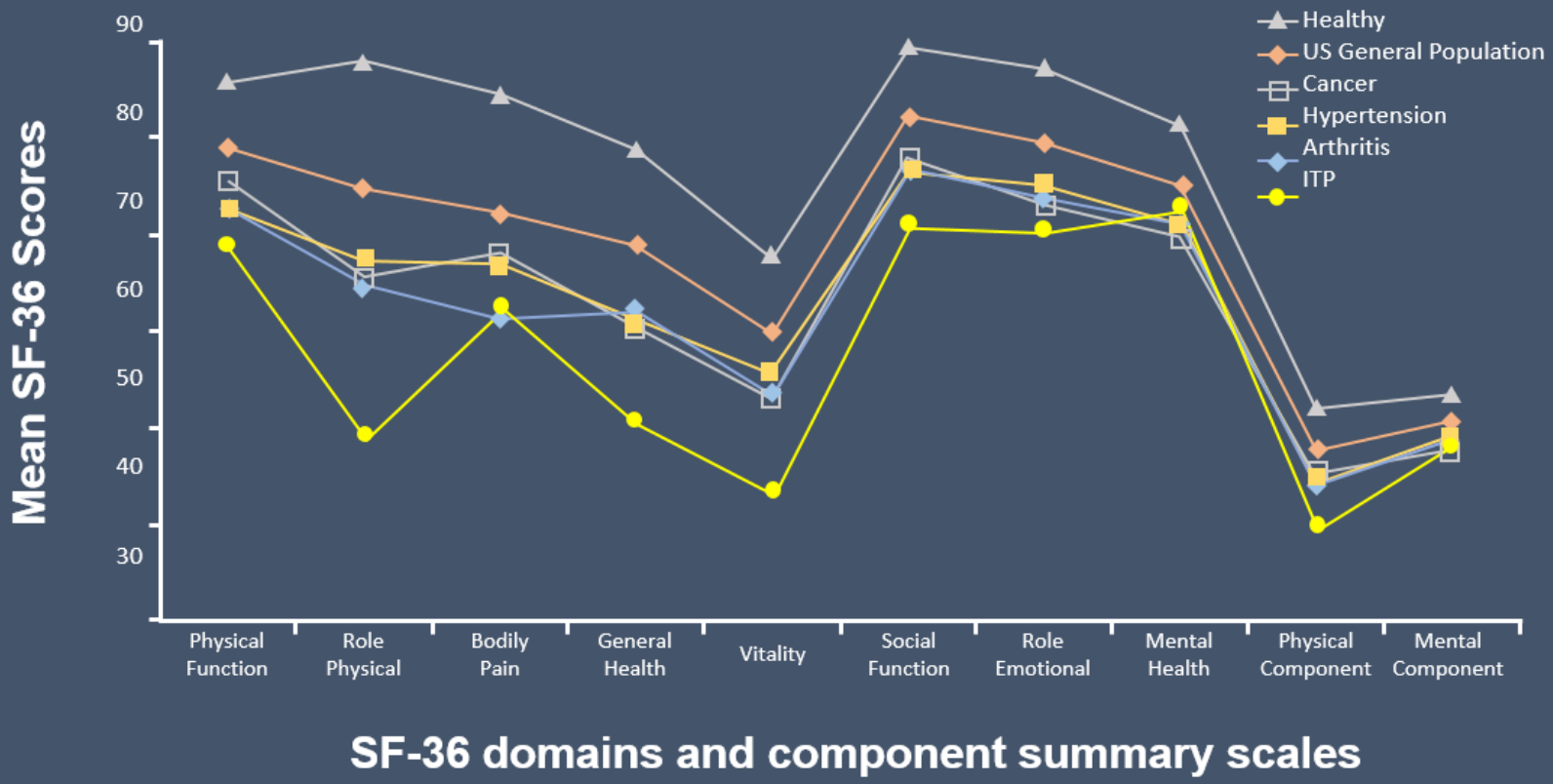
Cooper N *et al*. *Am J Hematol* 2021;96:188-98 & 199-207

QoL in ITP compared to other persons

- Five cross-sectional studies
- >3000 ITP patients
- Comparison groups either in study or population surveys
- QoL tools
  - SF-36
  - Fear-of-bleeding / bother-by-treatment questions
  - Fatigue score
  - ITP-PAQ
  - Others
- All studies showed reduced HRQoL compared to general population or healthy controls

Zhou *et al. Eur J Haematol* 2007; 78: 518-23, McMillan *et al. Am J Hematol* 2008; 83: 150-4, Snyder *et al. Curr Med Res Opin* 2008; 24: 2767-76, Sarpatwari *et al. Br J Haematol* 2010; 151: 189-91, Newton *et al.* Eur J Haematol 2011; 86: 420-9, Brown *et al. BMC Blood Dis* 2012; 12: 2-8

ITP and HRQoL compared to patients with other chronic conditions

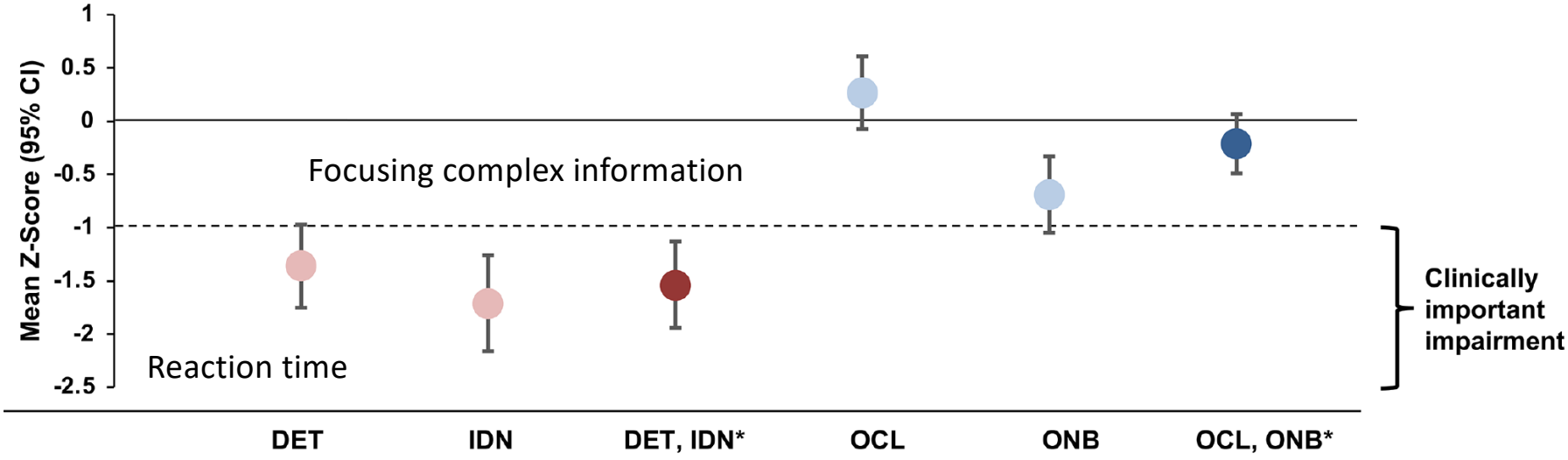


McMillan R *et al. Am J Hematol* 2008; **83**: 150–4

Neuropsychological burden in ITP

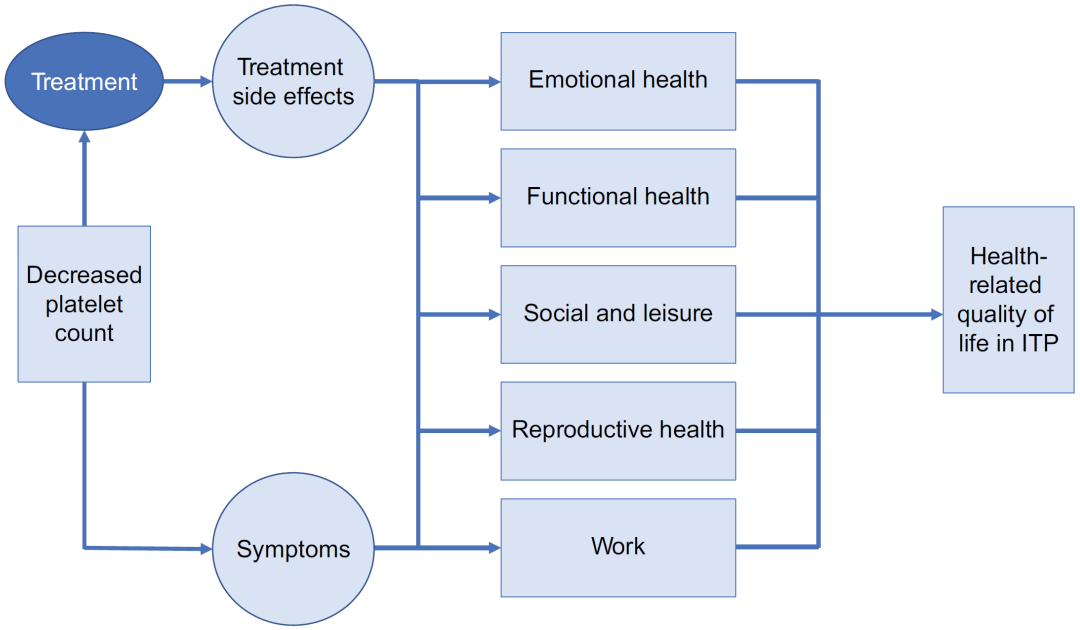
- LUNA 2 study (Phase 1/2)
- 49 pts neuropsychology assessment at baseline
- Normalized to general population - z-score
- ≤ 1 considered clinical relevant
- The magnitude / types of cognitive changes reflects those seen in
  - Moderate – severe depression
  - Chronic fatigue syndrome

Kuter D *et al*. *BJH* 2024;205:291-99



Major determinants of reduced HRQoL in ITP

- **Fatigue**
- Bleeding symptoms
- Fear, anxiety, depression
- Bother of disease and treatment effects on health
- Side effects of treatment
- Absences from work
- Reproductive health



Mathias SD *et al*. *Health Qual Life Outcomes* 2008;6:13

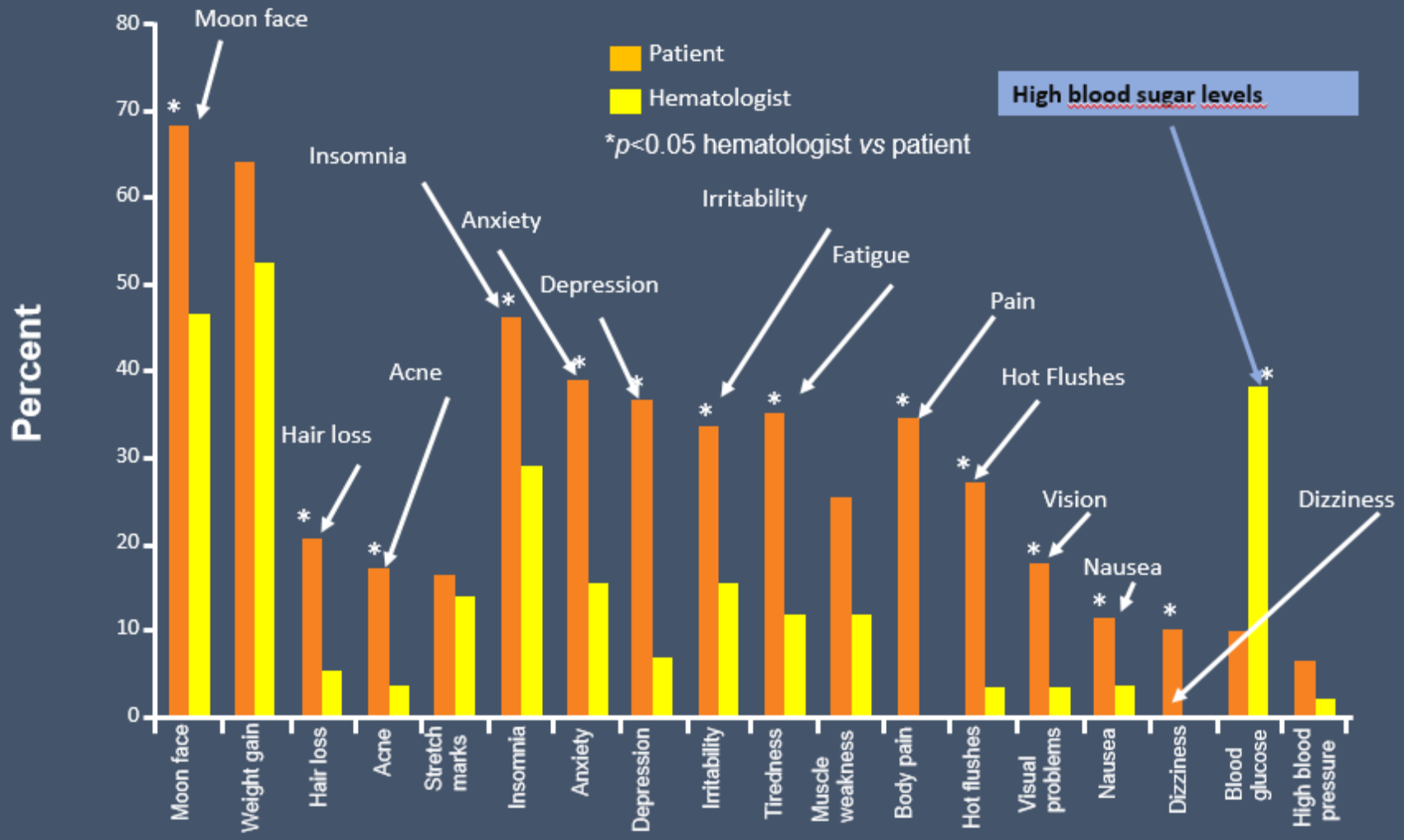
Platelet count and QoL in ITP

	Platelet count (x 10^9/L)					
ITP-PAQ:	≤10 (*n*=25)	11–29 (*n*=75)	30–49 (*n*=109)	50–99 (*n*=210)	100–149 (*n*=139)	≥150 (*n*=444)
Symptoms	45.2	60.5	64.7	68.0	73.8	78.7
Fatigue	49.5	57.3	56.2	58.9	62.1	70.6
Bother	48.7	71.2	65.9	75.6	79.3	83.1
Activity	56.0	70.0	67.0	73.9	78.7	81.0
Psychological	59.6	69.9	70.1	73.8	79.9	80.5
Fear	73.0	81.2	80.9	81.4	84.3	85.5
Overall quality of life	47.7	56.1	55.6	56.4	58.7	57.9
Social activity	63.5	78.3	78.0	79.7	82.9	83.5
Work	77.3	83.3	81.4	87.2	86.0	88.1
Women's reproductive health	47.4	58.3	60.1	68.2	66.7	71.9
Menstrual symptoms	46.9	55.1	60.8	63.6	62.6	71.2
Fertility	58.3	66.9	63.8	71.4	67.9	72.2

PAQ; Patient Assessment Questionnaire

Snyder CF *et al. Curr Med Res Opin* 2008; 24: 2767-76

How doctors and ITP patients rate steroid side effects



Guidry *et al. Eur j Haematol* 2009; **83**: 175-82

Burden of fatique in ITP

bjh review

Fatigue in immune thrombocytopenia

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[1]Department of Haematology, St James's University Hospital, Leeds, and [2]Department of Haematology, The Royal London Hospital, London, UK

Summary

Fatigue is an important aspect of health-related quality of life from the patient perspective and can have significant socio-economic consequences. It is a common feature of chronic illnesses and a significant number of both adults and children with immune thrombocytopenia (ITP) suffer from fatigue. Reliable, validated fatigue scales have been developed for use in ITP. These will facilitate future investigation of its pathogenesis and the effectiveness of intervention. Acute inflammation acts on neural and endocrine systems resulting in 'sickness behaviour', an adaptive response to infection and injury. Inflammation is also thought to cause fatigue in chronic disease and immune dysregulation in ITP appears to have a number of pro-inflammatory components. Clinicians should consider fatigue when assessing the burden of disease. Although effective ITP-directed therapy can improve fatigue, a number of fatigue-directed strategies may also need to be considered.

Keywords: immune thrombocytopenia, fatigue, inflammation, aetiology, quality of life.

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder associated with a reduced platelet count and may present with bruising and bleeding. Primary (idiopathic) ITP is rare, with an incidence of approximately 4–6 per 100 000 per year (Gernsheimer, 2008; Schoonen *et al*, 2009). Bleeding risk rises as the platelet count falls and for patients with a platelet count $<30 \times 10^9$/l, risk of fatal haemorrhage (usually intracranial) has been estimated at 0·016–0·039 cases per patient-year, although factors such as age also affect risk (Cohen *et al*, 2000). However, many have only minor mucosal bleeding or a tendency to bruise easily, one quarter are asymptomatic at presentation and those with mild disease do not usually require treatment. ITP is not purely a bleeding disorder and, paradoxically, an increased rate of venous thrombosis has been observed (Severinsen *et al*, 2011). Patient-reported outcomes help quantify the impact of a disease and its treatments on well being, daily life and physical, psychological and social functioning (Mathias *et al*, 2008). These are typically assessed with a health-related quality of life (HRQoL) questionnaire and HRQoL has been shown to be significantly reduced in patients with ITP compared to controls (McMillan *et al*, 2008; Snyder *et al*, 2008). In one study, HRQoL was similar to patients with diabetes mellitus and worse than those with other chronic diseases including hypertension, arthritis and cancer (McMillan *et al*, 2008).

Fatigue is one of the most common and distressing symptoms for patients with a chronic disease. It is a frequent symptom of autoimmune disorders and affects 80–93% of patients with rheumatoid arthritis (Huyser *et al*, 1998), 50–92% with systemic lupus erythematosis (SLE) (Schmeding & Schneider, 2013) and 68% with primary biliary cirrhosis (Cauch-Dudek *et al*, 1998). The negative impact of fatigue on task completion makes it an important public health issue, and in the United States, workers with fatigue cost employers $136·4 billion annually in lost productive time (Ricci *et al*, 2007). Patients with ITP also complain of fatigue and many feel that they have less energy when the platelet count is low (Cines & Bussel, 2005; Newton *et al*, 2011). We aim to review the evidence that ITP results in fatigue, the reasons why fatigue could develop and future prospects for research and clinical practice.

How do you define and measure fatigue?

Historically, studies of physical illness have rarely addressed fatigue, possibly because it is a subjective complaint that is difficult to define and measure. This lack of a clear and widely accepted definition is illustrated by cancer-related fatigue, for which 24 different definitions have been put forward by experts (Barsevick *et al*, 2010). Fatigue would be typically defined as extreme and persistent tiredness, weakness or exhaustion – mental, physical or both (Dittner *et al*, 2004). This is usually experienced in the absence of any excessive expenditure of energy as a cause and is often associated with decreased functioning, e.g. difficulty completing tasks.

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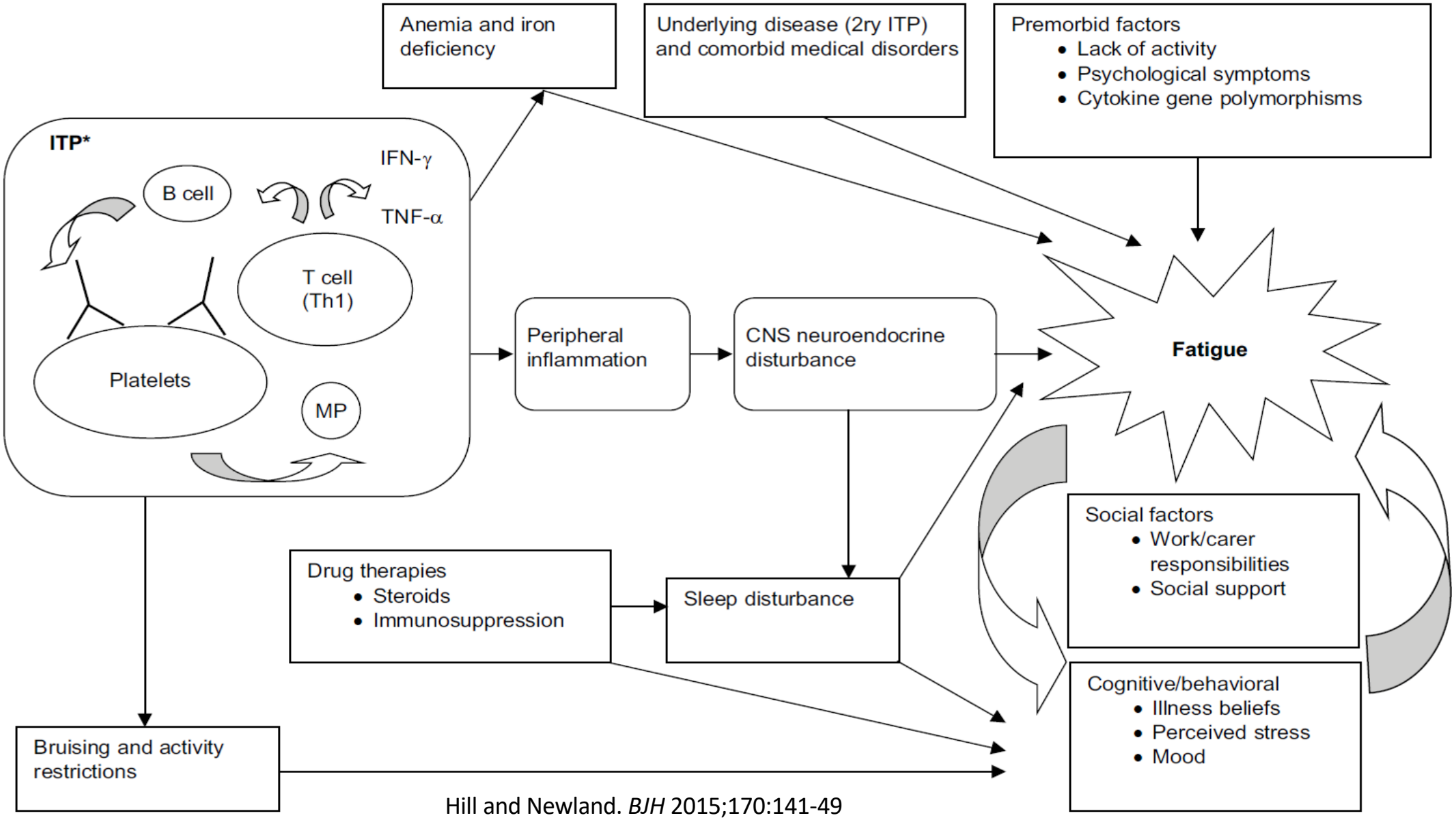
British Journal of Haematology, 2015, **170**, 141–149
First published online 30 March 2015
doi: 10.1111/bjh.13385

bjh BRITISH JOURNAL OF HAEMATOLOGY

- Frequent (22-39%)
- Among the worst scoring QoL domains (as in other diseases)
- Leads to frequent work / school abscences
- Generally no or only modest improvements with available therapies
- Causes are probably complex

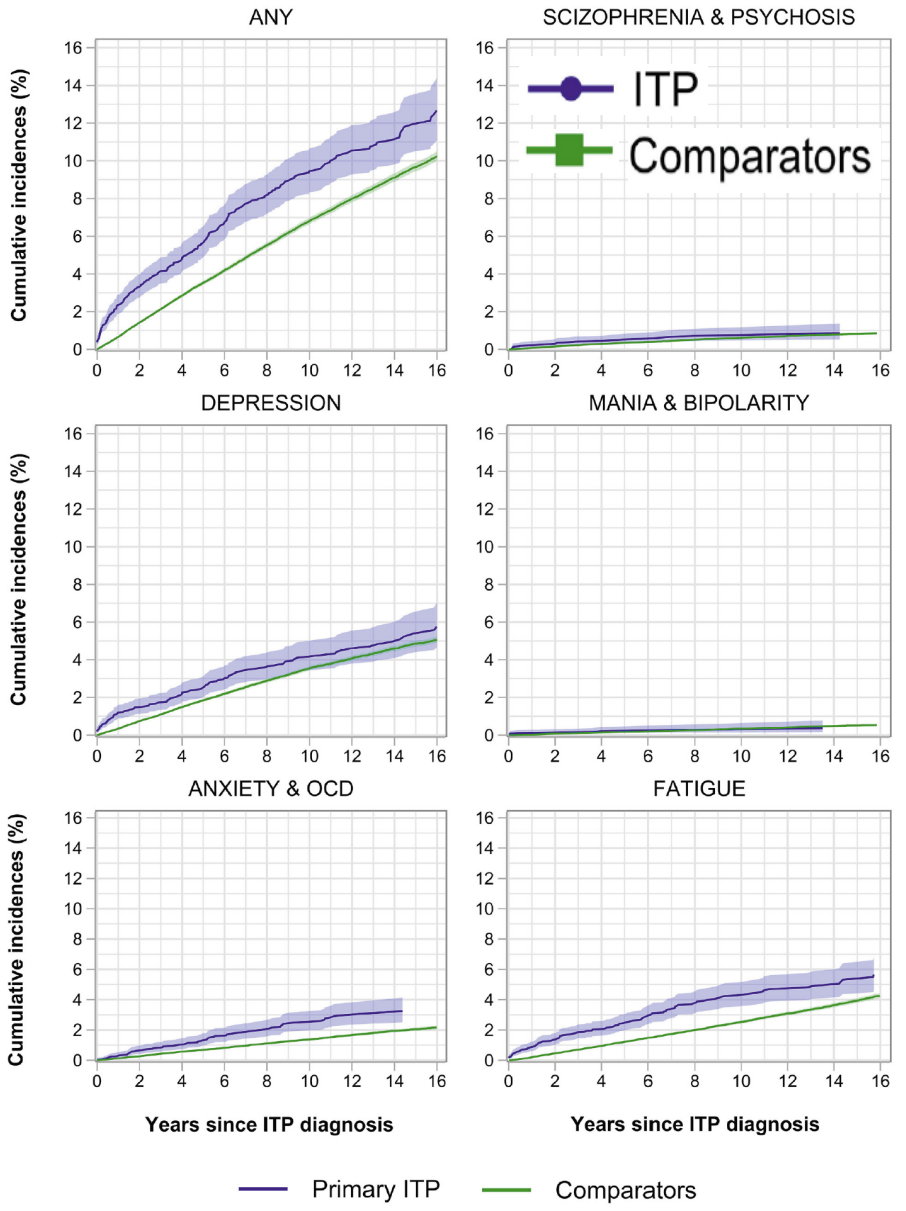
Hill and Newland. *BJH* 2015;170:141-49



Hill and Newland. *BJH* 2015;170:141-49

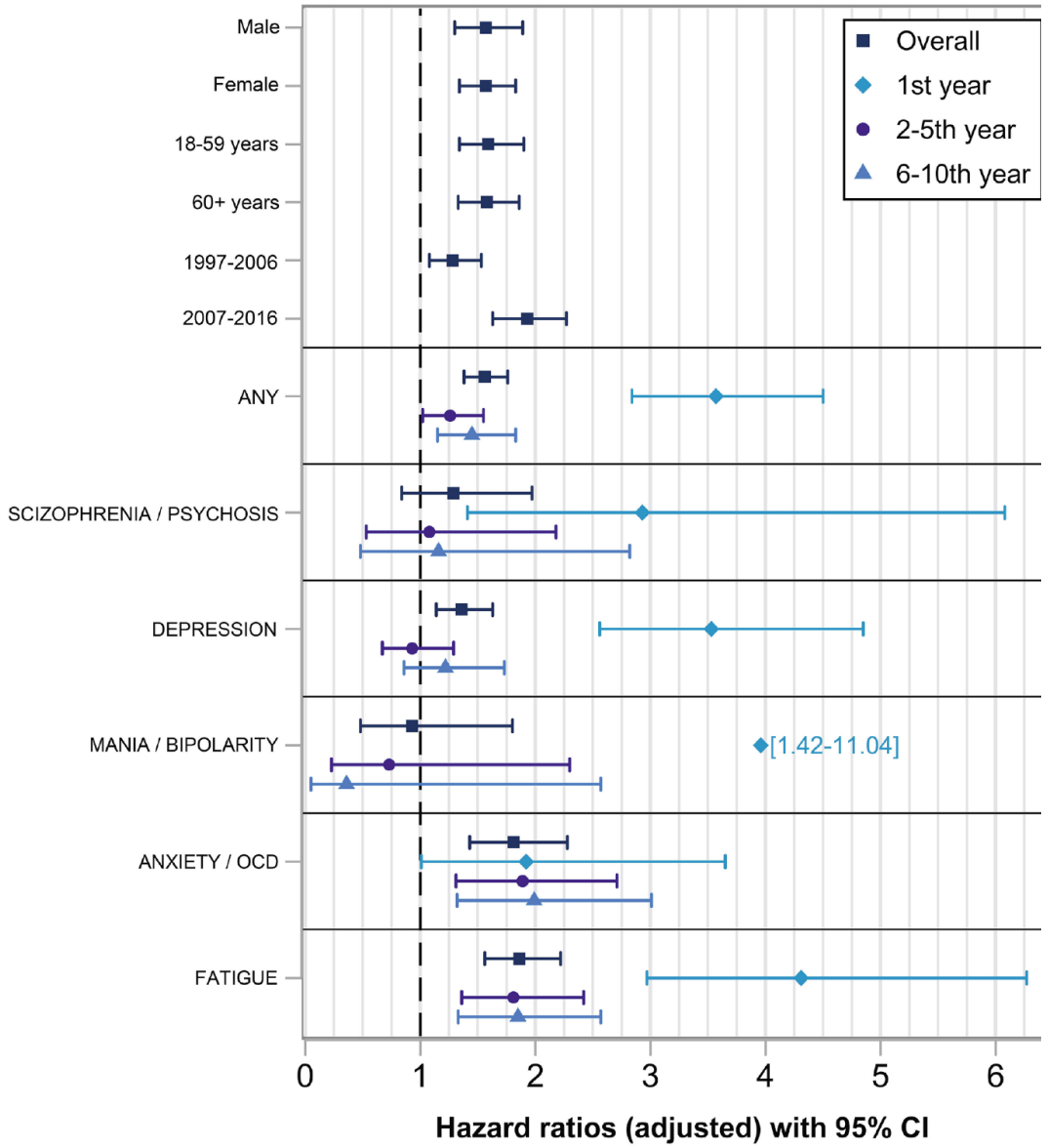
HOSPITAL REGISTERED MENTAL HEALTH CONDITIONS IN ITP - CIs

- **Primary ITP 3,749**
- **Comparators 149,849**



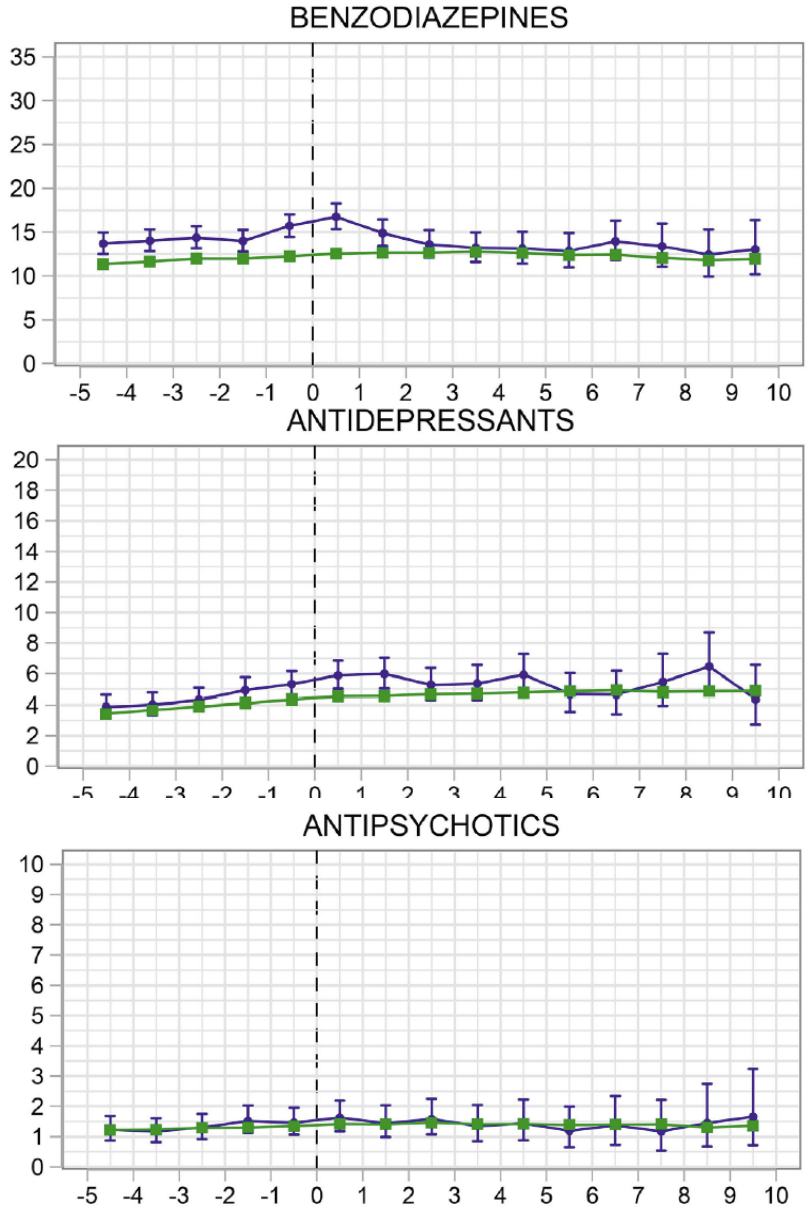
Mannering N *et al*. Haematologica, 2024; 109(1): 2944-54

HOSPITAL REGISTERED MENTAL HEALTH CONDITIONS IN ITP - HRs



Mannering N *et al*. Haematologica, 2024; 109(1): 2944-54

PSYCHOTROPHIC DRUG USAGE IN RELATION ITP DIAGNOSIS



Mannering N *et al*. Haematologica, 2024; 109(1): 2944-54

Goals of ITP management

- Stop bleeding
- Prevent new (serious) bleeding
- Reduce symptoms
- Individualize

- **Optimize Health-Related Quality of Life (HRQoL)**

- What are the options for the latter?

Optimizing HRQOL

- First do no harm
- Use a tolerable treatment that works
- Shared decision making
- Manage complications and comorbidity
- Gain new evidence

First do no harm

CLINICAL GUIDELINES

blood advances

Check for upd

American Society of Hematology 2019 guidelines for immune thrombocytopenia

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Background: Despite an increase in the number of therapies available to treat patients with immune thrombocytopenia (ITP), there are minimal data from randomized trials to assist physicians with the management of patients.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the management of ITP.

Methods: In 2015, ASH formed a multidisciplinary guideline panel that included 8 adult clinical experts, 5 pediatric clinical experts, 2 methodologists with expertise in ITP, and 2 patient representatives. The panel was balanced to minimize potential bias from conflicts of interest. The panel reviewed the ASH 2011 guideline recommendations and prioritized questions. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including evidence-to-decision frameworks, to appraise evidence (up to May 2017) and formulate recommendations.

Results: The panel agreed on 21 recommendations covering management of ITP in adults and children with newly diagnosed, persistent, and chronic disease refractory to first-line therapy who have non–life-threatening bleeding. Management approaches included: observation, corticosteroids, IV immunoglobulin, anti-D immunoglobulin, rituximab, splenectomy, and thrombopoietin receptor agonists.

Conclusions: There was a lack of evidence to support strong recommendations for various management approaches. In general, strategies that avoided medication side effects were favored. A large focus was placed on shared decision-making, especially with regard to second-line therapy. Future research should apply standard corticosteroid-dosing regimens, report patient-reported outcomes, and include cost-analysis evaluations.

Summary of recommendations

Background

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the University of Oklahoma Health Sciences Center (OUHSC). The guideline panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[1-4] The panel used the Grading of Recommendations

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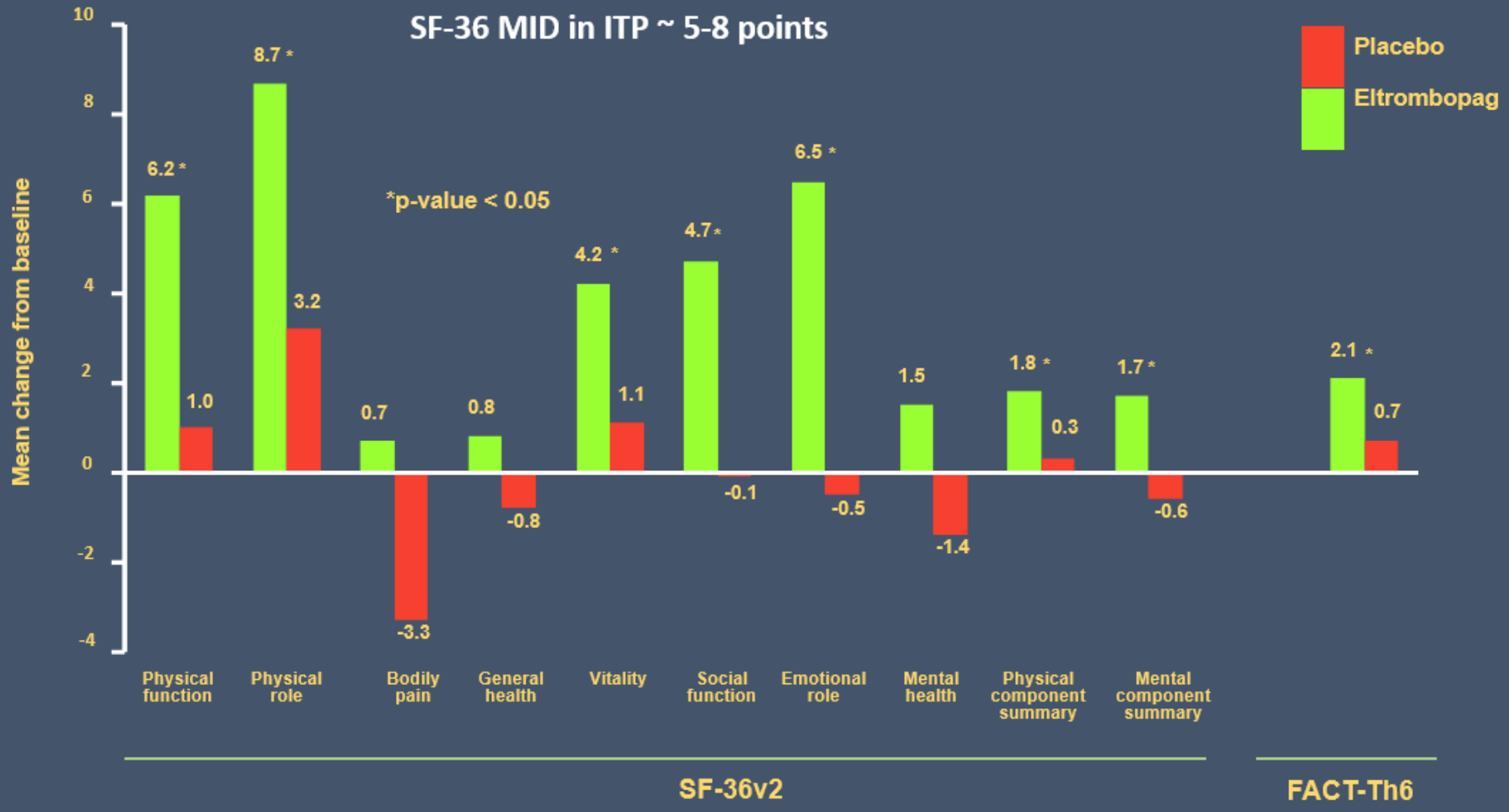
"Given the potential impact on mental health, the treating physician should conduct an assessment of health-related quality of life, depression, fatigue, mental status, etc) while patients are receiving corticosteroids."

- How about
  - Our advices?
  - Activity restrictions?
  - Monitoring?

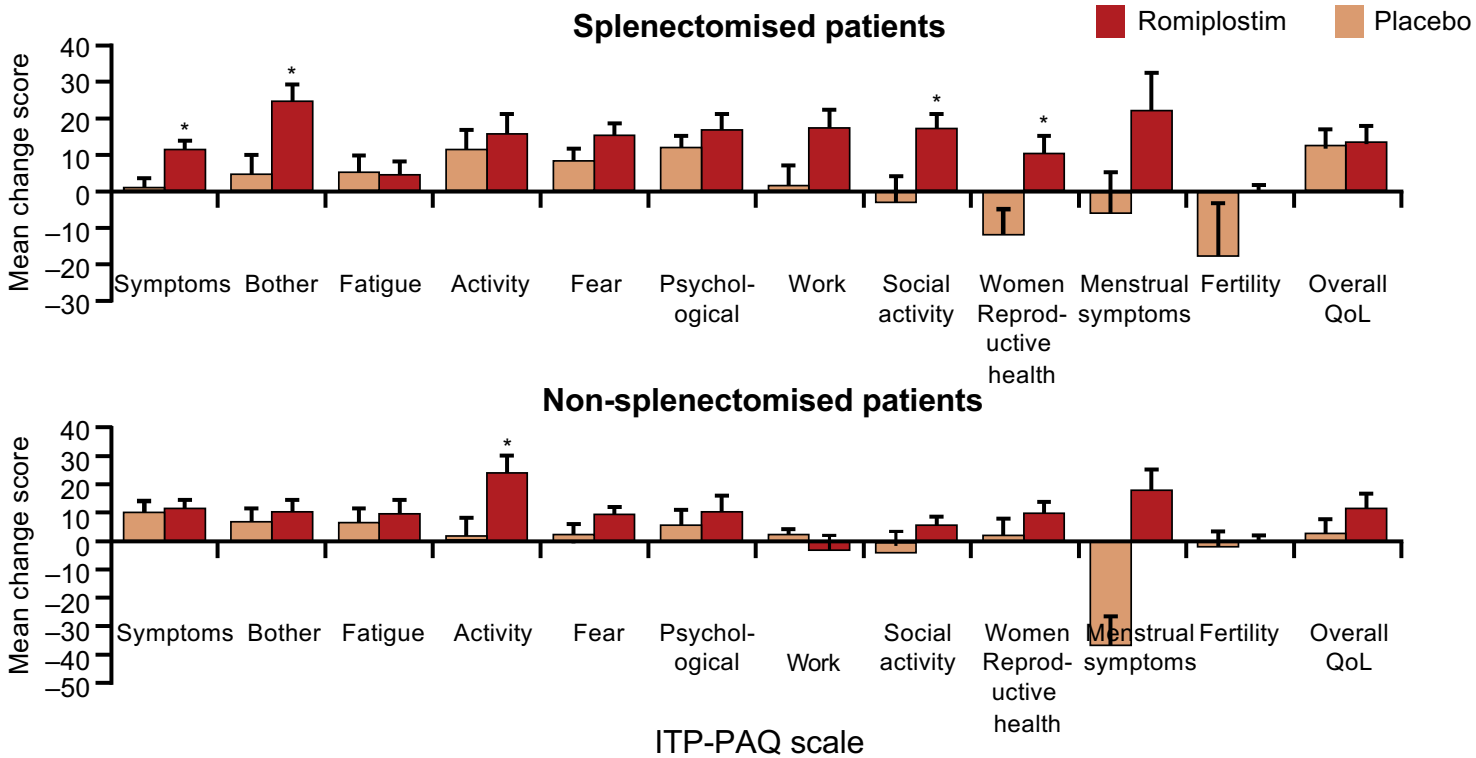
Tolerable treatments that works

Eltrombopag vs placebo – RAISE study
HRQoL changes from after 26 weeks – n=197



Cheng G *et al. Lancet* 2011; **377**: 393-402.

Romiplostim vs placebo
HRQoL changes after 24 weeks – n=125

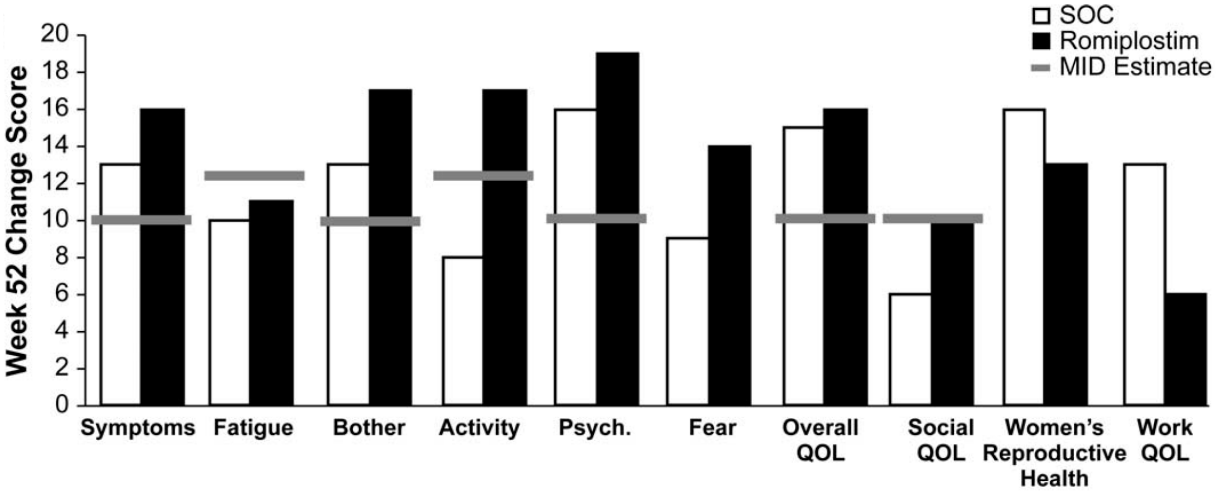


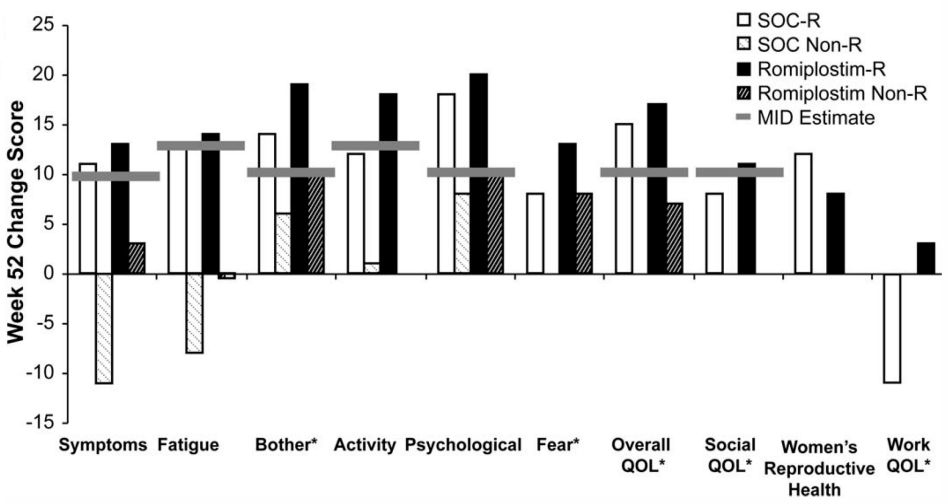
*$P < 0.05$

ITP-PAQ self-administered at BL, week 4, week 12, and week 24 of treatment

George J *et al.* *Br J Haematol* 2008; 144: 409-15

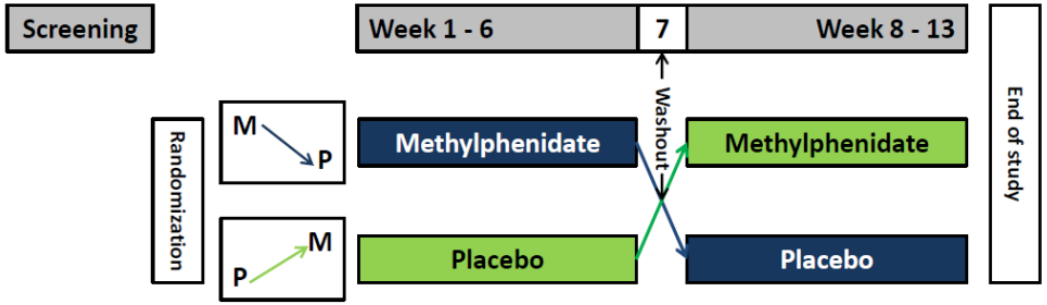
Romiplostim vs SOC
HRQoL changes after 52 weeks – non-splenectomized





Kuter DJ *et al. Am J Hematol* 2012; 87(5): 558-61

Gaining new evidence – are we targeting the right population?



Conclusions

- Burden of reduced HRQoL in adults with ITP is considerable
- Mental health in general is affected too
- Causes are complex
- Lack of prospective / longitudinal data from routine care / unselected populations
- Optimal management strategies to prevent or treat reduced HRQoL and its consequences are unknown
  - ITP directed therapy?
  - Psycho-social support?
  - E-tools?
  - ….