

Iron Therapy

Dr Kiran Desai

Consultant In Gastroenterology

Walsall Manor Hospital

CONFLICTS OF INTEREST

Vifor Pharma /Abbvie
consultant on their advisory board.

Aims

1. Why is it important to understand it better?
2. Understanding Iron metabolism.
3. When Oral Iron Works and when it does not!
4. When to use PRCs and when not!
5. Does Chronic Inflammation has impact on Iron absorption and how?
6. When to use IV Iron?
7. Dose of IV Iron
8. Risk Vs Benefits of IV Iron

PATHWAY.

On a lighter note!



Understanding Iron Absorption/Metabolism.

Dietary Factors

Iron Rich Foods
WholesomeBabyFoodGuide.com

Red Meat

Dark Leafy Greens

Egg Yolks

Quinoa

Broccoli

Poultry

Shellfish - oysters etc. (cooked @ 12 months+)

Grains

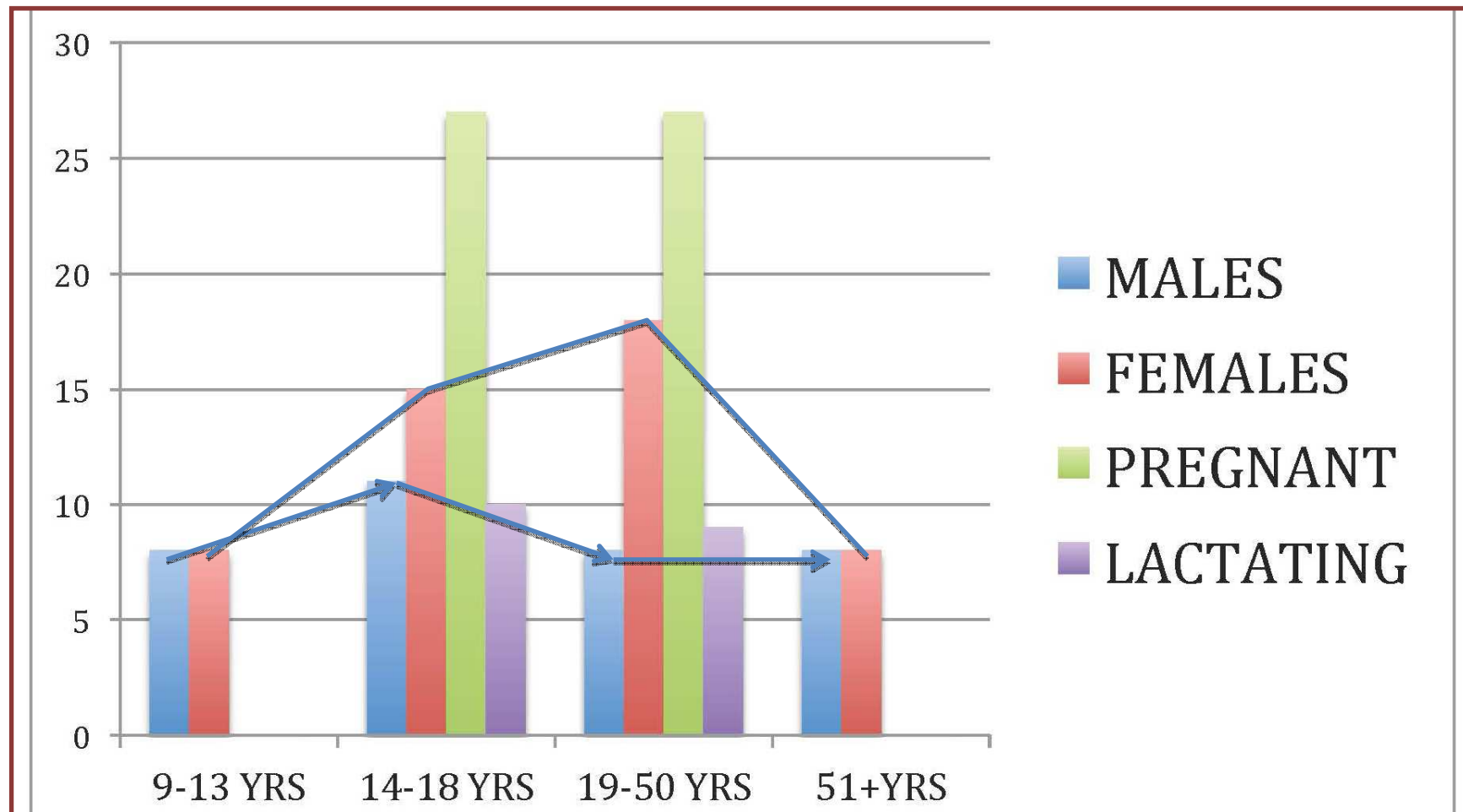
Dried Fruits

Legumes/Lentils

Vitamin C
Vitamin C helps the body absorb iron more efficiently

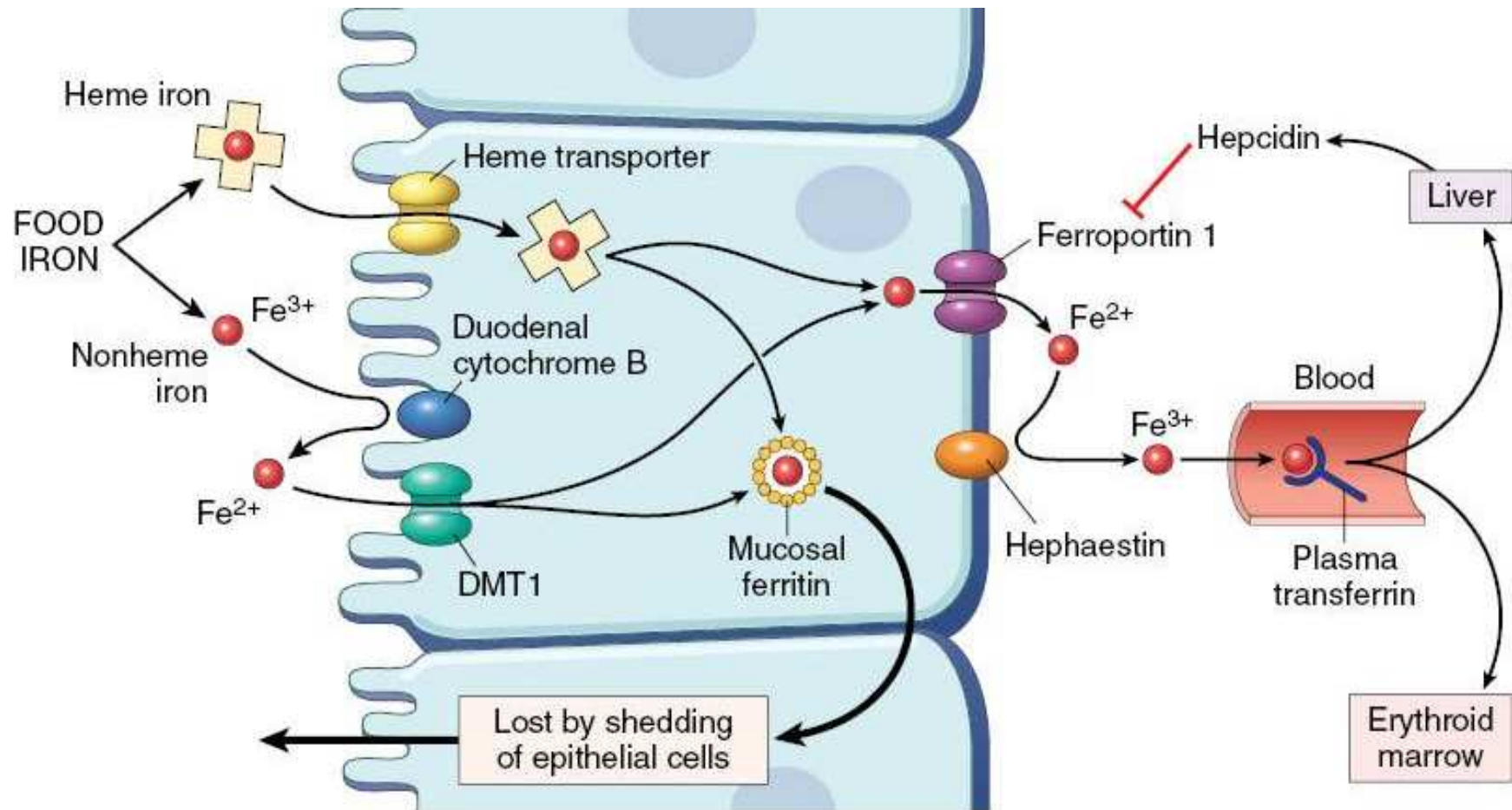
maggie mende 2013

Daily Recommended Iron Intake



Iron Absorption and Utilization

Iron Absorption

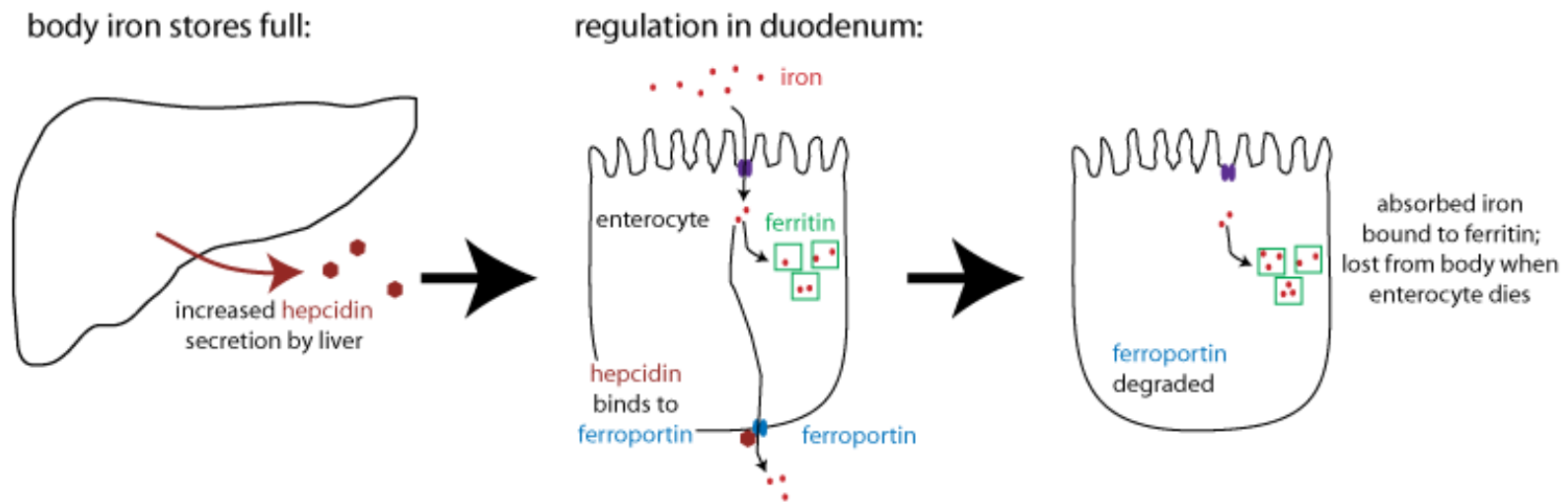


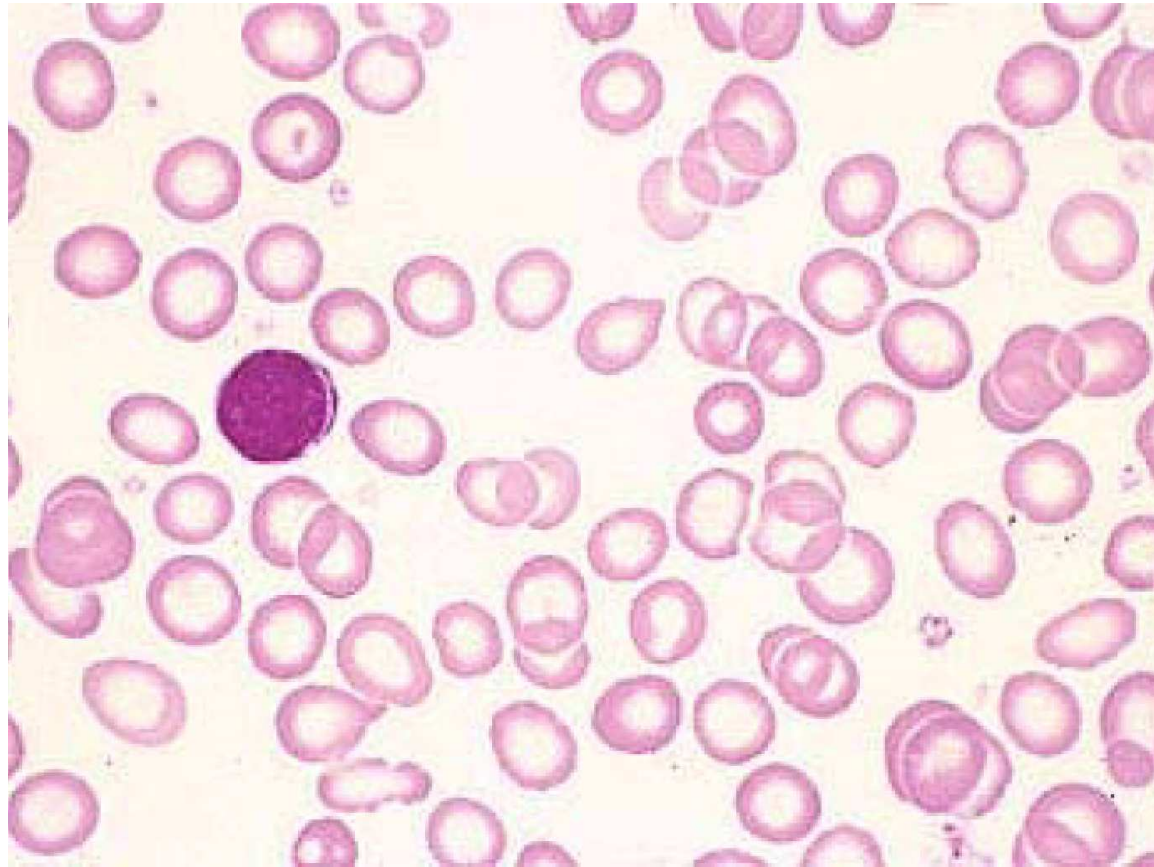
Iron Excretion

Small quantities are excreted by desquamation of GI epithelial cells.

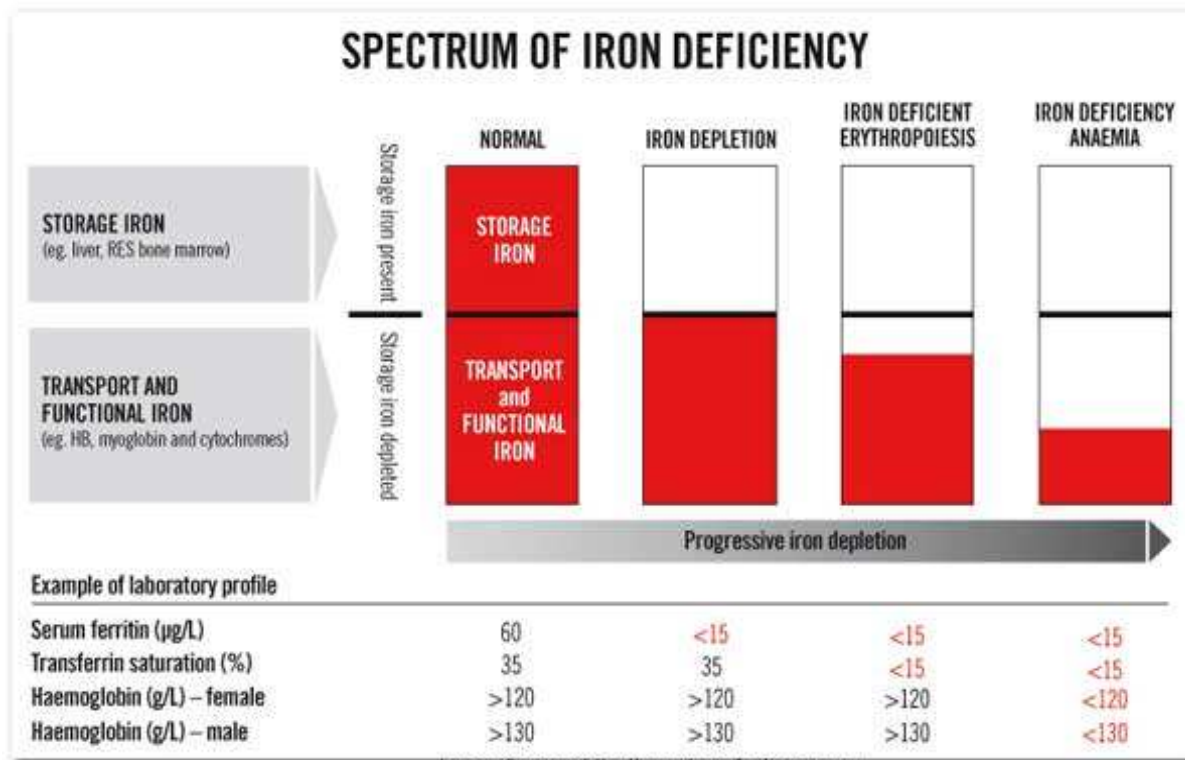
This is not dependent on Iron saturation.

Iron Replete state





Iron Deficiency



Iron Deficiency State

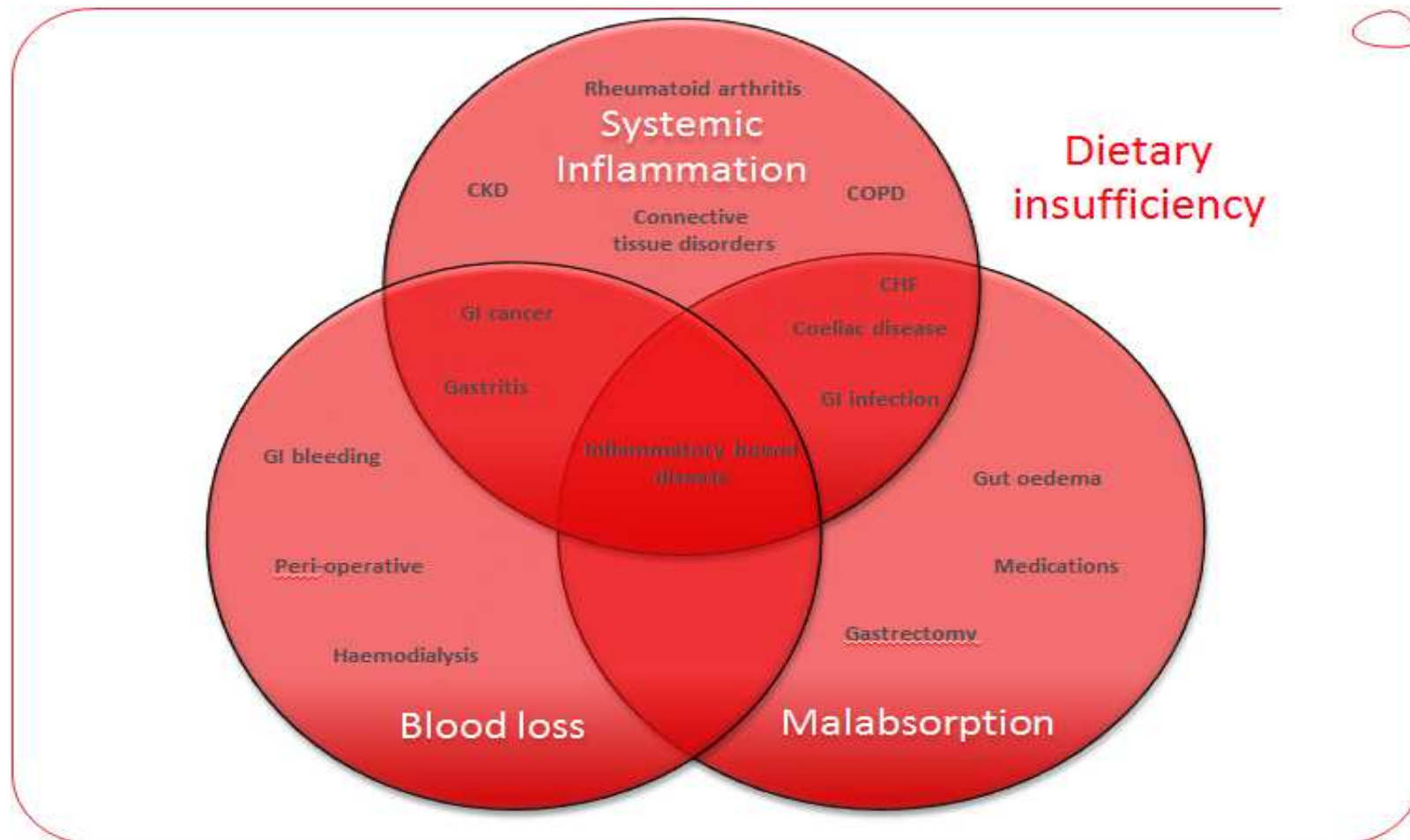
CAUSES OF IRON DEFICIENCY

UK/OTH/15/0045

Date of Preparation: February 2015

VIFOR PHARMA, THE PHARMA BUSINESS SECTOR OF THE GALENICA GROUP

Causes of IDA



THE SIZE OF THE CHALLENGE

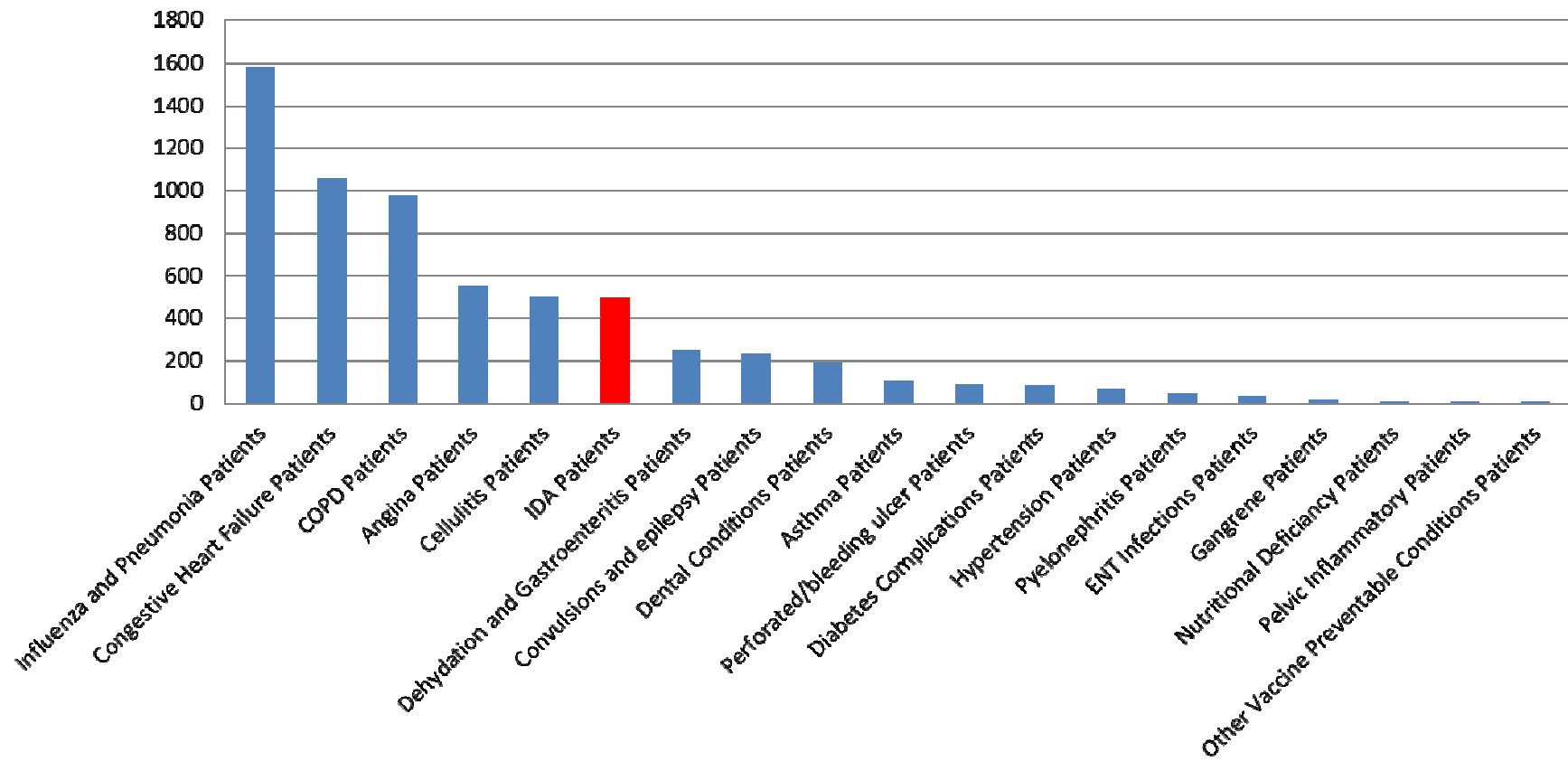
UK/OTH/15/0045

Date of Preparation: February 2015

VIFOR PHARMA, THE PHARMA BUSINESS SECTOR OF THE GALENICA GROUP

IDA is the 6th Most Common Cause of Potentially Avoidable Admissions in the Over 75yrs¹

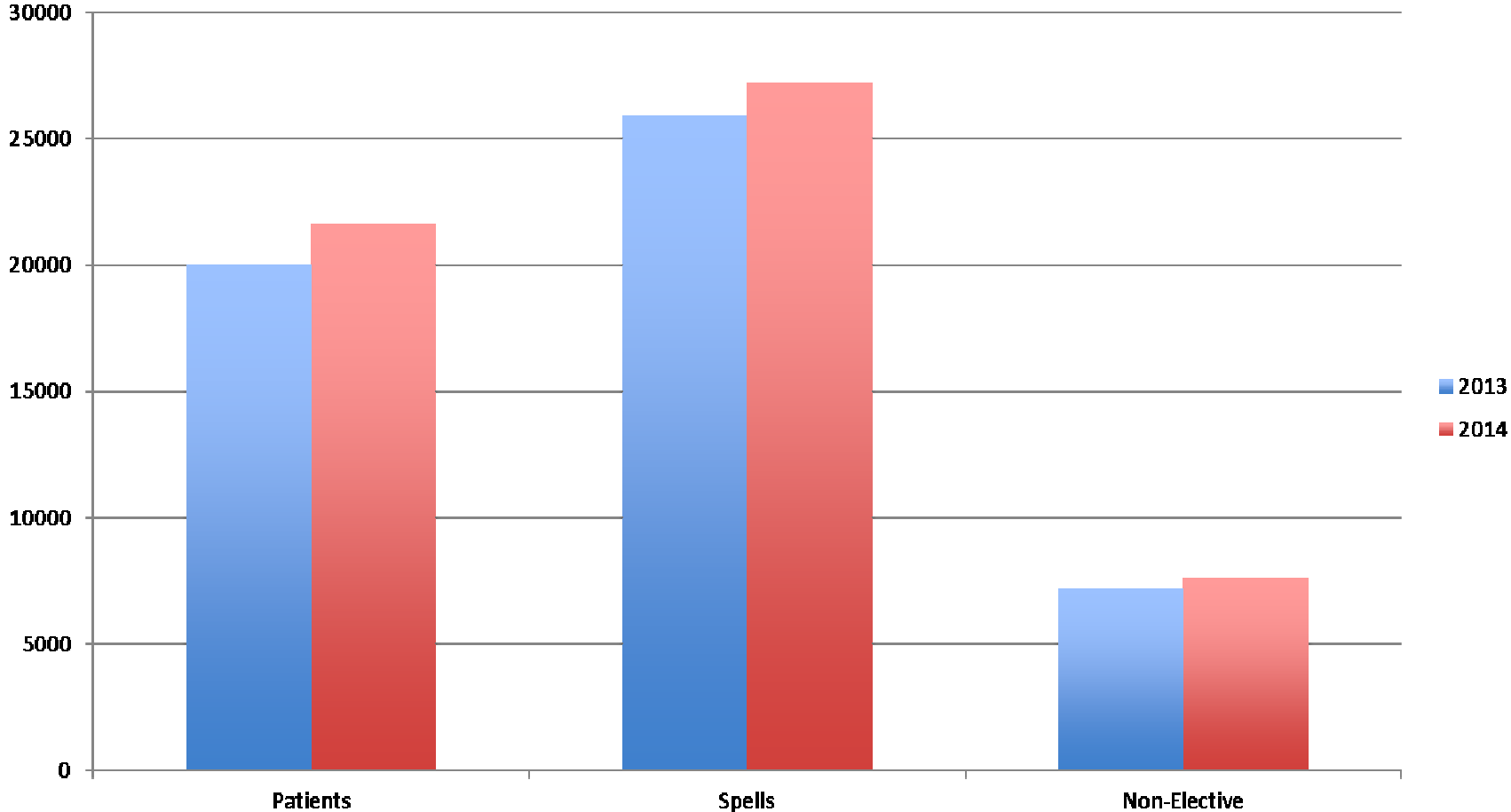
ACSC Conditions 75 and Over / 100,000 Population (National)



UK/OTH/15/0045
Date of Preparation: February 2015

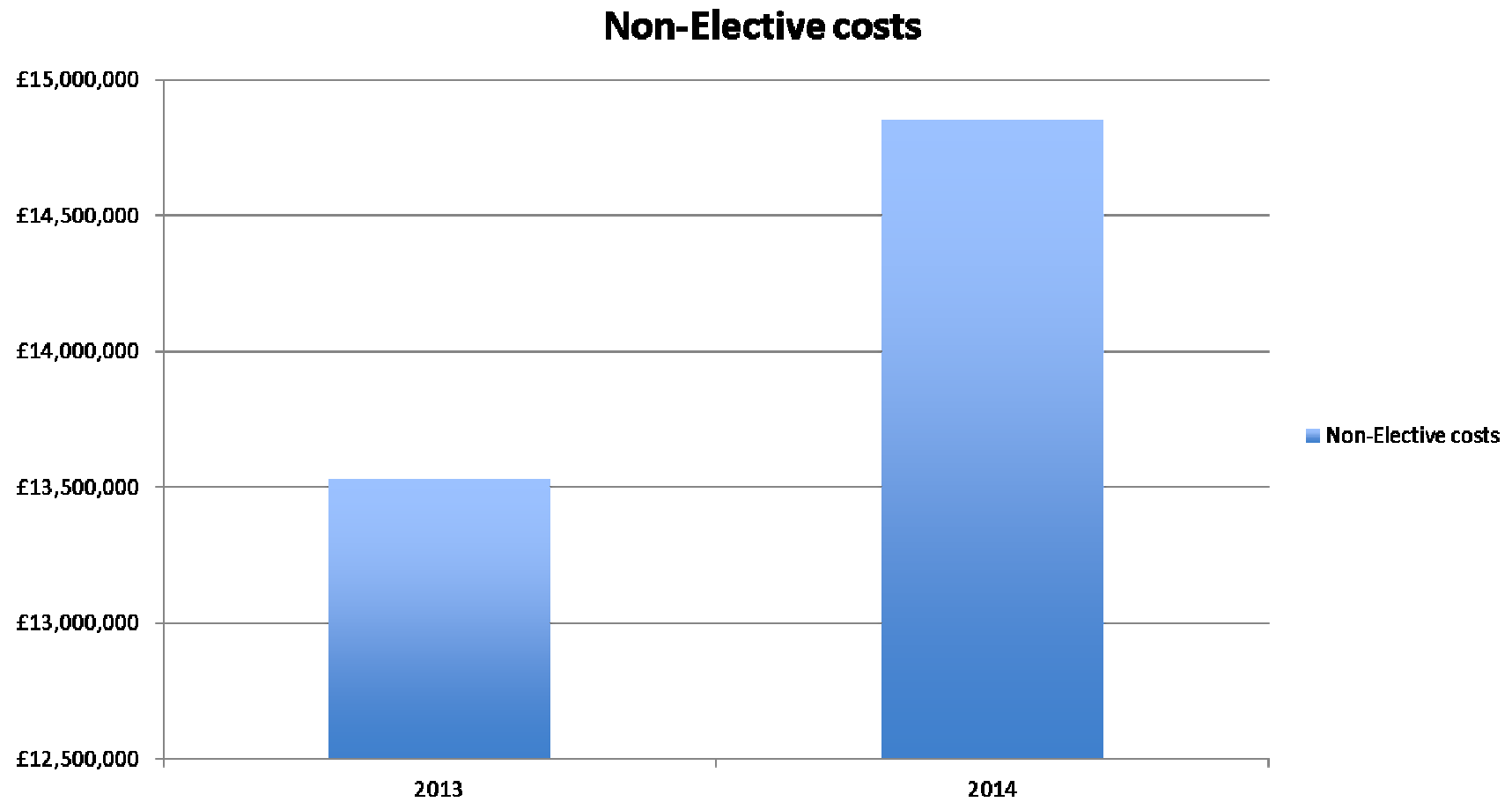
1. Data on File, Harvey Walsh Ltd (Source: HES Data, England 2013/14)

Over 75yrs Health Episode Statistics 2013/2014¹

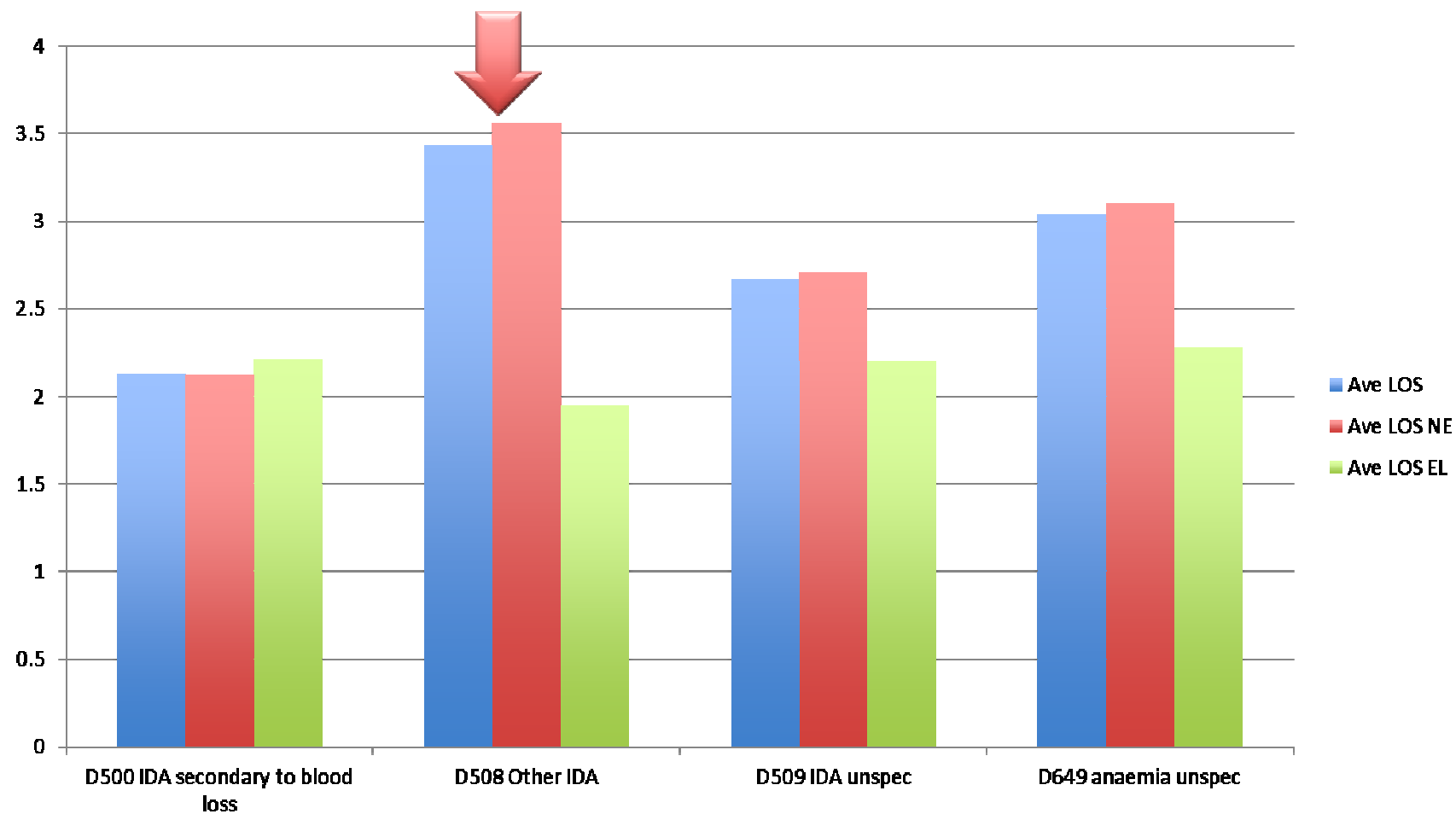


1.Data on File, Harvey Walsh Ltd (Source: HES Data, England 2013/14)

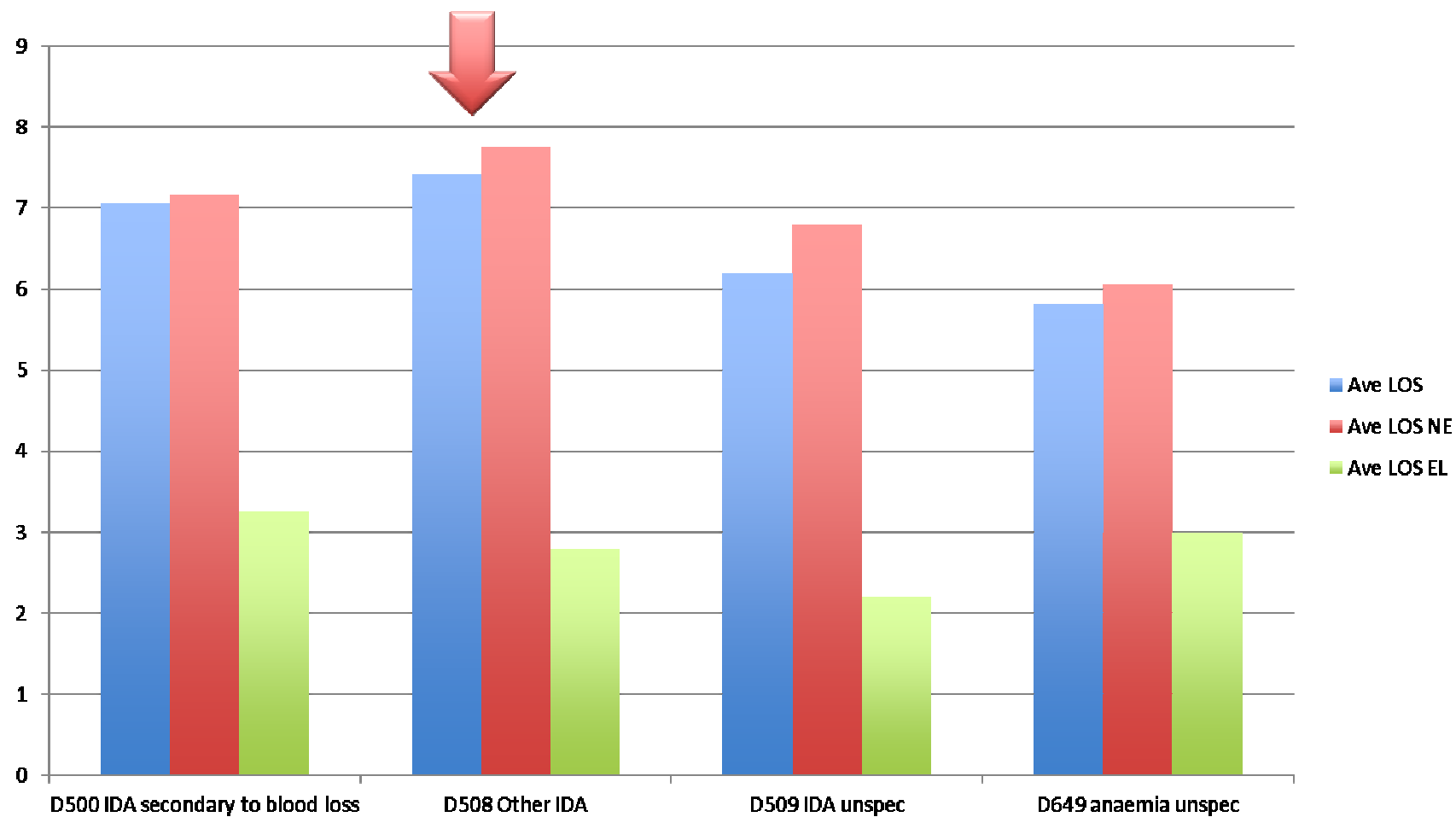
Cost to NHS!!



Length of stay- Under 75 years of age



Length of stay- Age- 80 years and above



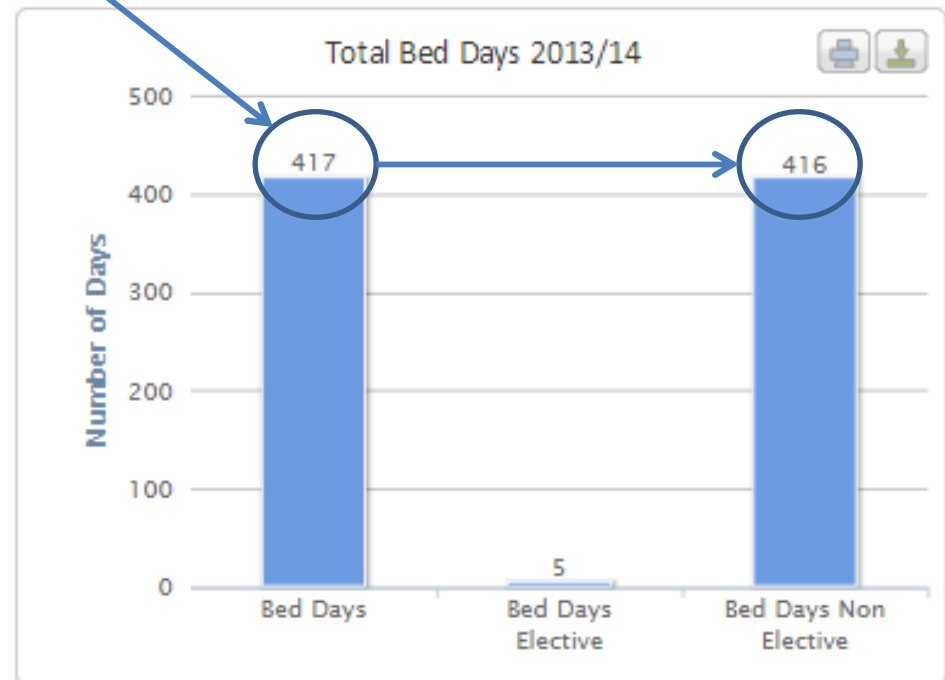
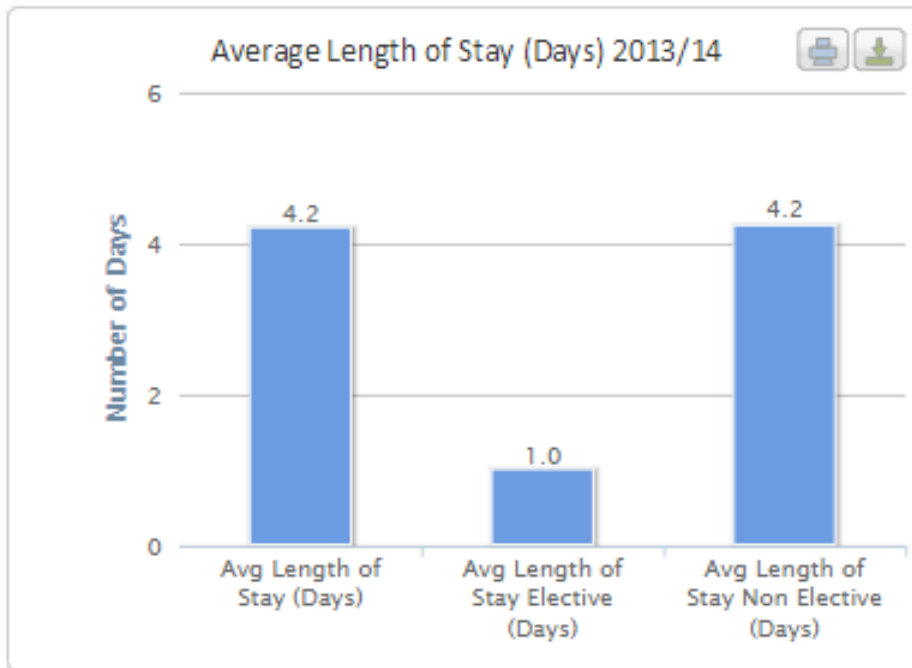
Primary Diagnosis of IDA (ICD10)
downloaded 24/04/2015

Walsall Healthcare NHS Trust

What is the impact of IDA on bed capacity?

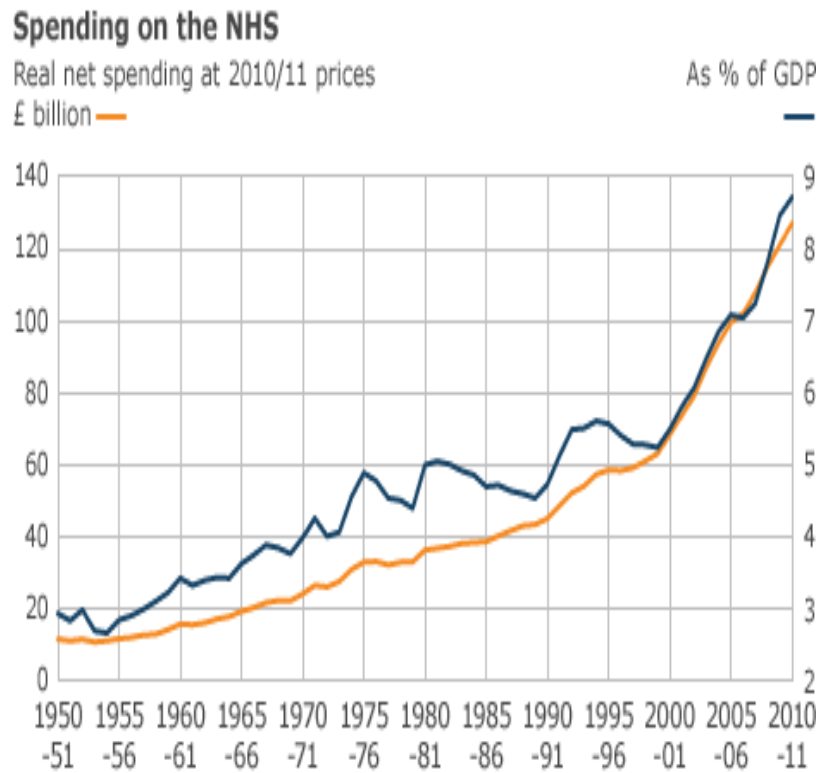
Number of bed days where patients have been coded as primary diagnosis of IDA

The Majority of this is attributed to the non-elective cohort



What does this mean?

Increased cost to the healthcare Poor patient care



Source: King's Fund



Prevalence of Anaemia Older People

US NHANES III¹

- Anaemia in **11% of men & 10% of women ≥65 years**; ~20% by age 80 years
- 20% due to iron deficiency; 24% due to anaemia of inflammation

UK SACN 2010²

- Anaemia in **52% of men & 39% of women** in institutions
- Anaemia in **13-38% of free-living adults ≥75 years**
- ID in 12-14% of free-living women ≥75 years

US Women's Health and Ageing Studies³

- Anaemia in **13.3%** of community-dwelling women ≥70 years
- ID in 5.8%
- IDA in 3.8%
- ID accounted for >1/4 of all anaemia

HEPCIDIN

Date of Preparation October 2014

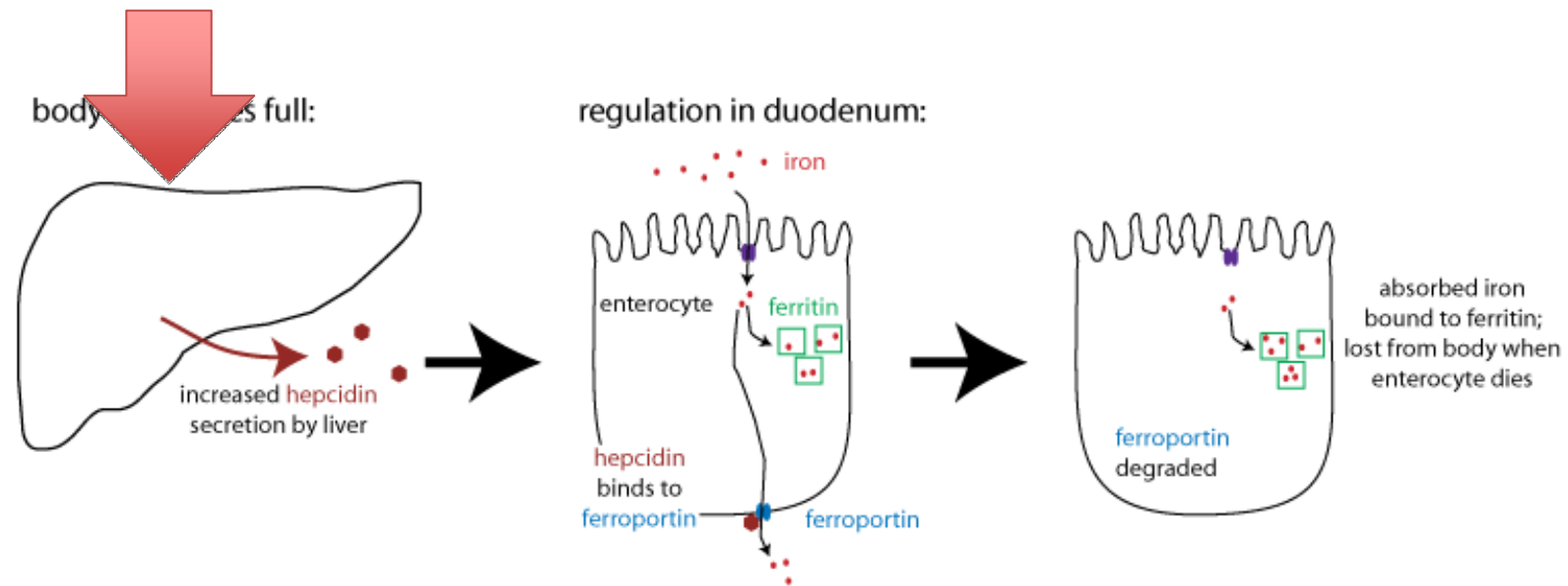
VIFOR PHARMA, THE PHARMA BUSINESS SECTOR OF THE GALENICA GROUP

Hepcidin

- Hepcidin is understood to be the principal regulator of iron homeostasis.
- Peptide hormone produced by the liver.
- Acts to reduce iron uptake by enterocytes in the GI tract and block the release of iron from hepatocyte and macrophage stores.
- Levels are high when the body is iron replete and low when the body is iron deficient.
- Hepcidin is also an acute-phase reactant.
- Systemic inflammation, and co-morbid inflammatory conditions lead to the up-regulation of the hormone hepcidin which inhibits the utilisation of iron in the body.

Role of Systemic Inflammation

INFLAMMATION



IMPACT OF ANAEMIA ON COMORBIDITIES AND FUNCTION

UK/OTH/15/0045

Date of Preparation: February 2015

VIFOR PHARMA, THE PHARMA BUSINESS SECTOR OF THE GALENICA GROUP

Mortality

- Anaemia has been found to be significantly associated with **increased mortality** in community-dwelling elderly people,^{1,2,3} Nursing Home residents^{4,5} & hospitalized patients.⁵
- Anaemia of inflammation has been shown to be significantly associated with increased mortality in community-dwelling, older, disabled women.⁶
- Some evidence that **improving Hb improves survival**.^{5,7}

Frailty

- Anaemia significantly & independently associated with:
 - Frailty¹
 - Higher rate of disability, poor performance & reduced muscle strength²
 - Decline in physical performance over time³
 - Longer stay in hospital (25 v 13 days)⁴

Chronic Heart Failure

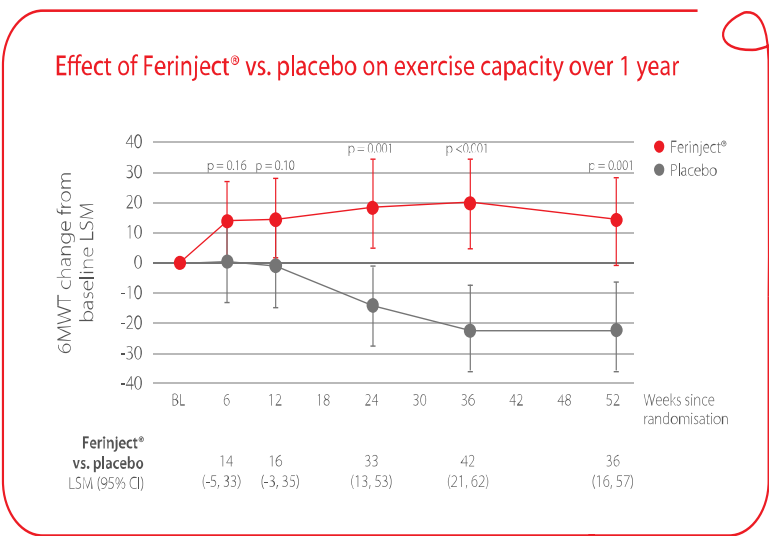
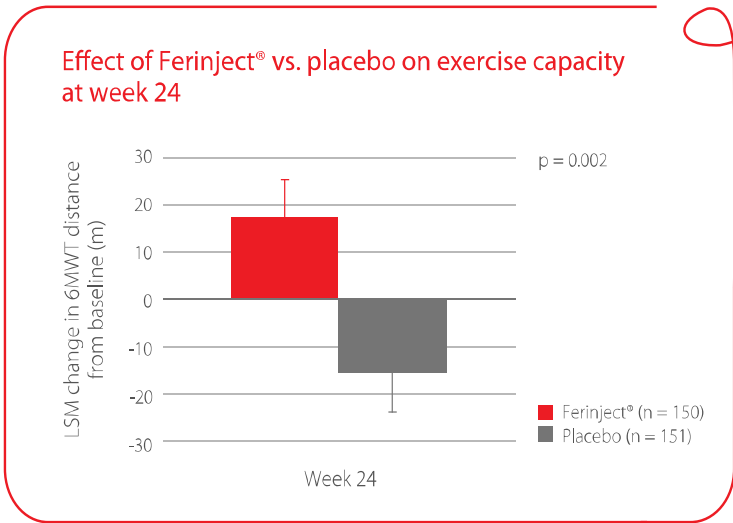
Chronic Heart Failure (CHF)

- Iron deficiency present in **35-50% of CHF patients**.^{1,2,3}
- Iron deficiency independently associated with risk of death in patients with heart failure.^{1,2,3}
- IV iron treatment improves symptoms, functional class and exercise tolerance in patients with CHF.^{4,5,6}
- IV iron shown to reduce the risk of hospitalization due to worsening CHF.⁶
- IV iron reduces BNP levels.⁷

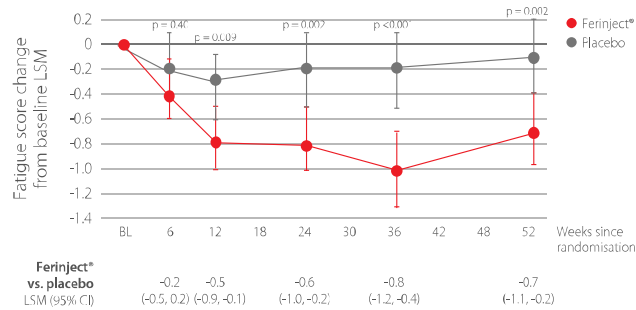
CONFIRM-HF¹

A 52 week, placebo-controlled study to assess the effect of IV iron (Ferinject[®]) on exercise capacity, symptoms, QoL and safety in patients with CHF and iron deficiency.

Ferinject[®] significantly improved exercise capacity at week 24 vs placebo, with a significant and sustained improvement in 6MWT during 1 year.

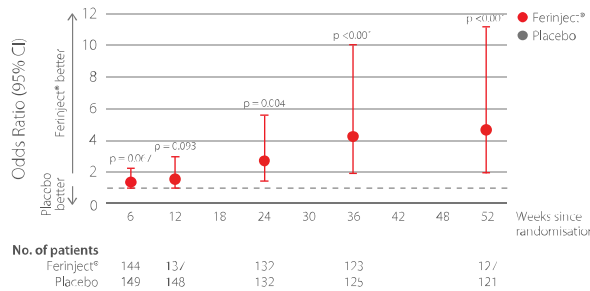


Effect of Ferinject® vs. placebo on fatigue score



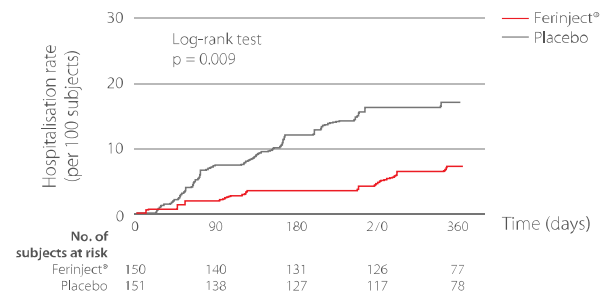
Ferinject® significantly improved quality of life, measured by the Patient Global Assessment (PGA), fatigue scores and Kansas City Cardiomyopathy Questionnaire (KCCQ) scores.¹

Effect of Ferinject® vs. placebo on NYHA functional class



Ferinject® significantly improved NYHA class from week 24 onwards vs placebo.¹

Ferinject® vs. placebo on time to first hospitalisation due to worsening HF



Ferinject® was associated with a reduction in the risk of first hospitalisation due to worsening CHF.¹

TREATMENT OF IDA

UK/OTH/15/0045

Date of Preparation: February 2015

VIFOR PHARMA, THE PHARMA BUSINESS SECTOR OF THE GALENICA GROUP

Iron Therapy

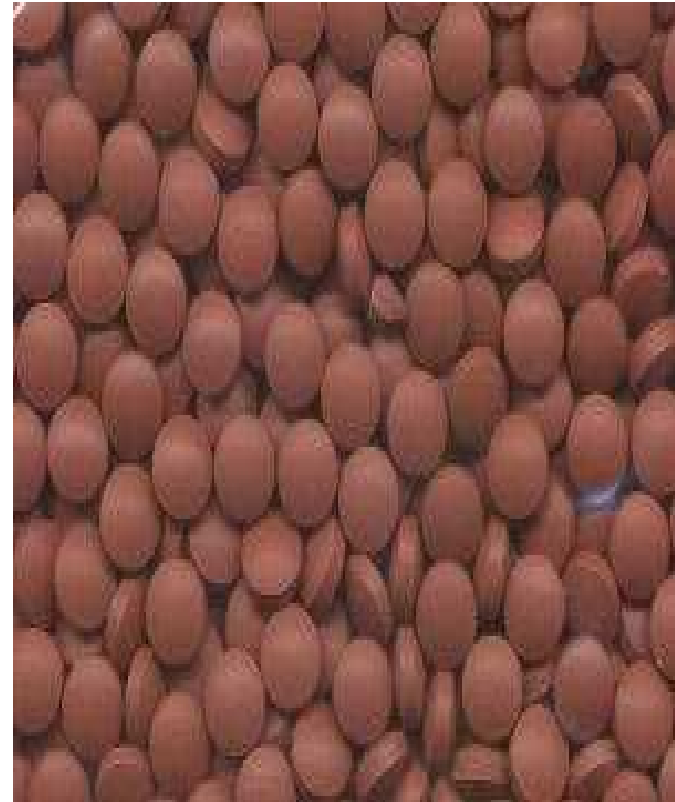
Enteral Iron Therapy

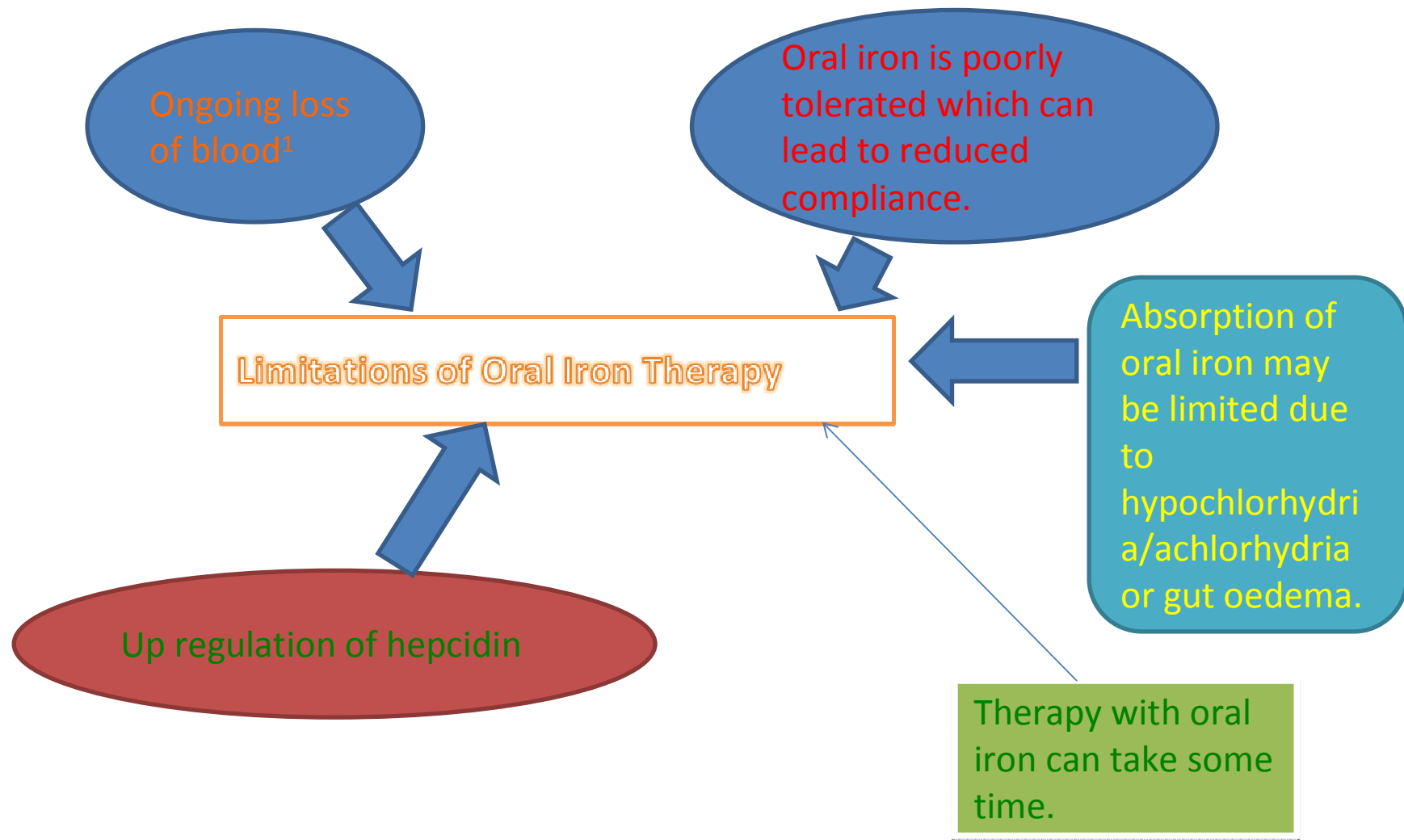
First line

Cost Effective

For How Long?

Till Hb is back to normal and
3 months to replenish Iron
Stores.





Treatment Options for ID/IDA

	Oral iron	IV iron	Blood transfusion
Advantages	Cost	High iron content	Essential in cases of cardiovascular instability ¹
	Non-invasive	100% bioavailable	Replaces RBCs
	Simple administration	Compliance	Compliance
	Convenient	Fast acting ²	
		Well tolerated ³	
Disadvantages	Intolerance	Potential adverse reactions	Potential transfusion reactions
	Potential poor compliance	Invasive	Invasive
	Risk of malabsorption in inflammatory conditions	Day case / inpatient	Day case / inpatient – secondary care input needed
	Slower to increase haemoglobin vs IV iron ²	Cost	Cost
	Interactions with common oral drugs		Limited supply
	Can delay investigative procedures, i.e. colonoscopies		Complex administration
	Can only absorb 10-20mg a day ³		

1. Goddard AF et al. Gut 2011;60:1309-1316
2. Kulnigg S et al. Am J Gastroenterol 2007;102: 1-11
3. Gasche C et al Inflamm Bowel Dis 2007; 13(12):1545-53
4. Restellini S et al. Aliment Pharmacol Ther 2013; 37:316-322

UK/OTH/15/0045 Date of Preparation: February 2015	Venofer ¹	Cosmofer ²	Ferinject ⁵
Maximum single dose	200mg 3x per wk	20mg/kg	20mg/kg, up to 1000mg
Test dose required	x	x	x
Infusion times	30 mins	4-6 hours	≤500mg - 6 mins >500mg - 15 mins
Use in children	x	≥14 years	≥14 years
Use in pregnancy	Not in 1 st trimester	Not in 1 st trimester	Not in 1 st trimester
Use in breastfeeding	✓	Not recommended	✓
Use with caution in asthma, eczema or other atopic allergy	✓	✓	✓
Use with caution in decompensated cirrhosis and hepatitis	✓	x	✓
Use with caution in rheumatoid arthritis with active inflammation	✓	✓	✓
Acute renal failure	✓	x	✓
Use with caution in patients with acute or chronic infection	✓	x	✓

1 Venofer Summary of Product Characteristics 2 Cosmofer Summary of Product Characteristics 3 Monofer Summary of Product Characteristics
4 Rienso Summary of Product Characteristics 5 Ferinject Summary of Product Characteristics

IV Iron Treatment Effectiveness

- Bypasses the limitations of oral iron, as it circumvents the gut.
- Quickly restores both available iron and iron stores.
- High levels of iron in cells up-regulate ferroportin channels, partially overcoming the hepcidin block, allowing release of iron from macrophages.

Safety of IV Iron

Historic Concerns of Parenteral Irons

- Many clinicians have experience historically with High Molecular Weight (HMW) dextran iron preparations.
- The unacceptably high risk of dextran-based anaphylactic reactions led to withdrawal from the European Market.
- More recent parenteral iron preparations are considered to be better tolerated than the HMW dextran irons.

Cost Effectiveness



Resource (1g)

	1g	
Cosmofer		Ferinject
79.7	Drug Cost per gram	140.06
79.7	Drug Cost per dose	140.06
10201.6	Drug cost per 128 patients	17927.68
5	Chair time (hours)	1.25
277.75	Chair cost (@£55.55/hour) per dose	69.4375
35552	Chair cost per 128 patients	8888
70.4	Nurse Cost (@£14.08/hour) per dose	17.6
9011.2	Nurse cost per 128 patients	2252.8
54764.8	Total Annual Cost	29068.48
427.85	Per Patient Cost	227.0975
	Total Saving	25696.32
37632	Total income 128 x SA04D @ £294	37632
-17132.8	Annual Cost -Annual Income (Trust Profit)	8563.52

Resource (1.5g)

	1.5g	
Cosmofer		Ferinject
79.7	Drug Cost per gram	140.06
119.55	Drug Cost per dose	210.09
15302.4	Drug cost per 128 patients	26891.52
5	Chair time (hours)	2.5
277.75	Chair cost (@£55.55/hour) per dose	138.875
35552	Chair cost per 128 patients	17776
70.4	Nurse Cost (@£14.08/hour) per dose	35.2
9011.2	Nurse cost per 128 patients	4505.6
59865.6	Total Annual Cost	49173.12
467.7	Per Patient Cost	384.165
	Total Saving	10692.48
37632	Total income 128 x SA04D @ £294	75264
-22233.6	Annual Cost -Annual Income (Trust Profit)	26090.88

Case scenarios

- Medical

27, M known to have severe UC, presents with Anaemia.

Hb 79,

MCV 63,

Fer 12

What treatment?

- Medical/Ortho

- 84, M with fall. #NOF.

Hb 81

MCV 66

Fer 31

What Treatment?

Case scenarios

- 74, M presents with IDA, new diagnosis of CRC.
- Due to have right hemicolectomy in 2 weeks?
- What treatment?

49, F with menorrhagia/DUB,
Hb 84

MCV/MCH – low

Fer 4

Due to have hysterectomy
in 6 weeks?

What treatment?

Could we use Iron to minimize blood transfusions

Medical-

Have a clear pathway of management of IDA, Improved access to IV Iron.

Obstetric-

Early access to Iron therapy.
Pathway

Surgical

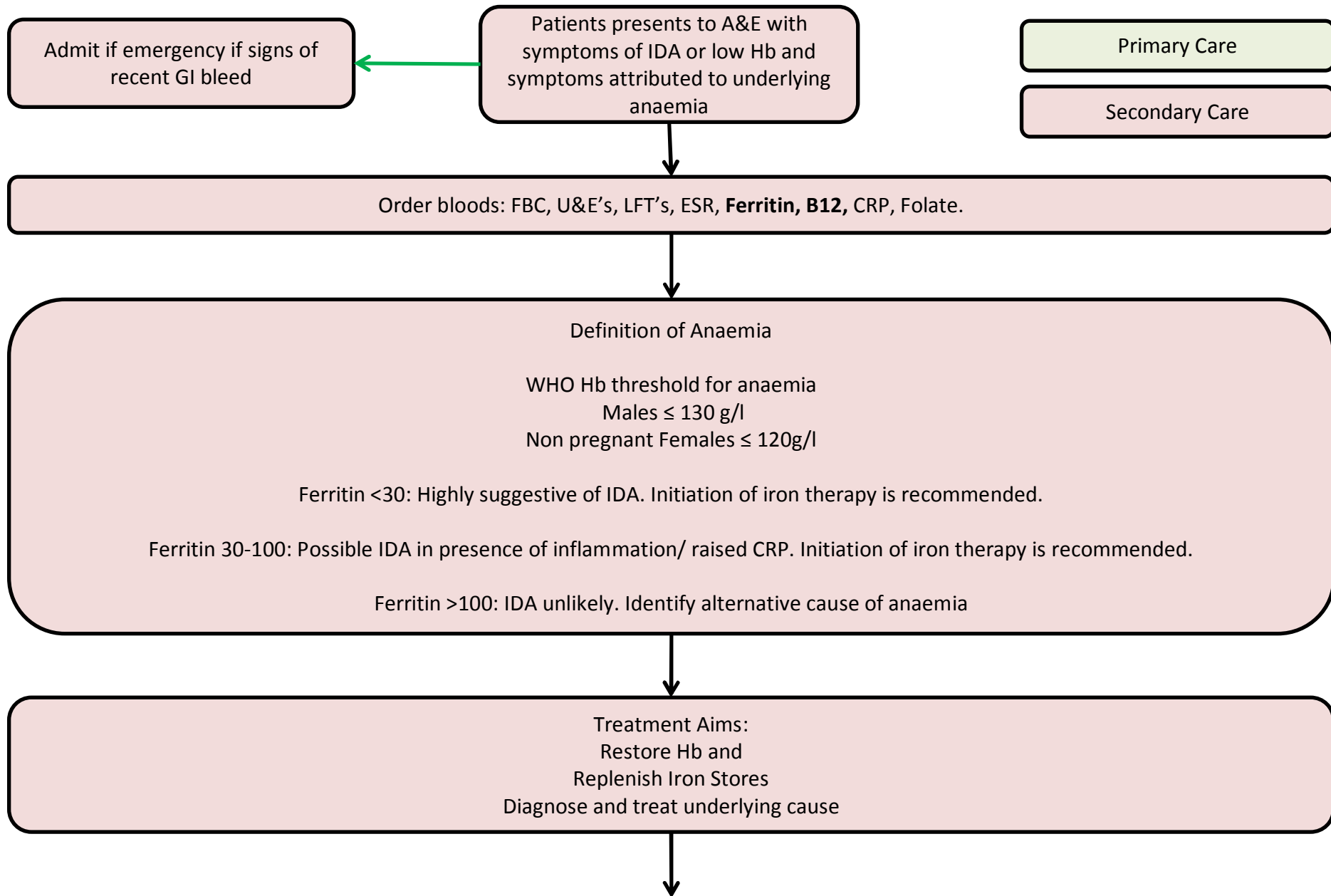
Emergency- Probably not

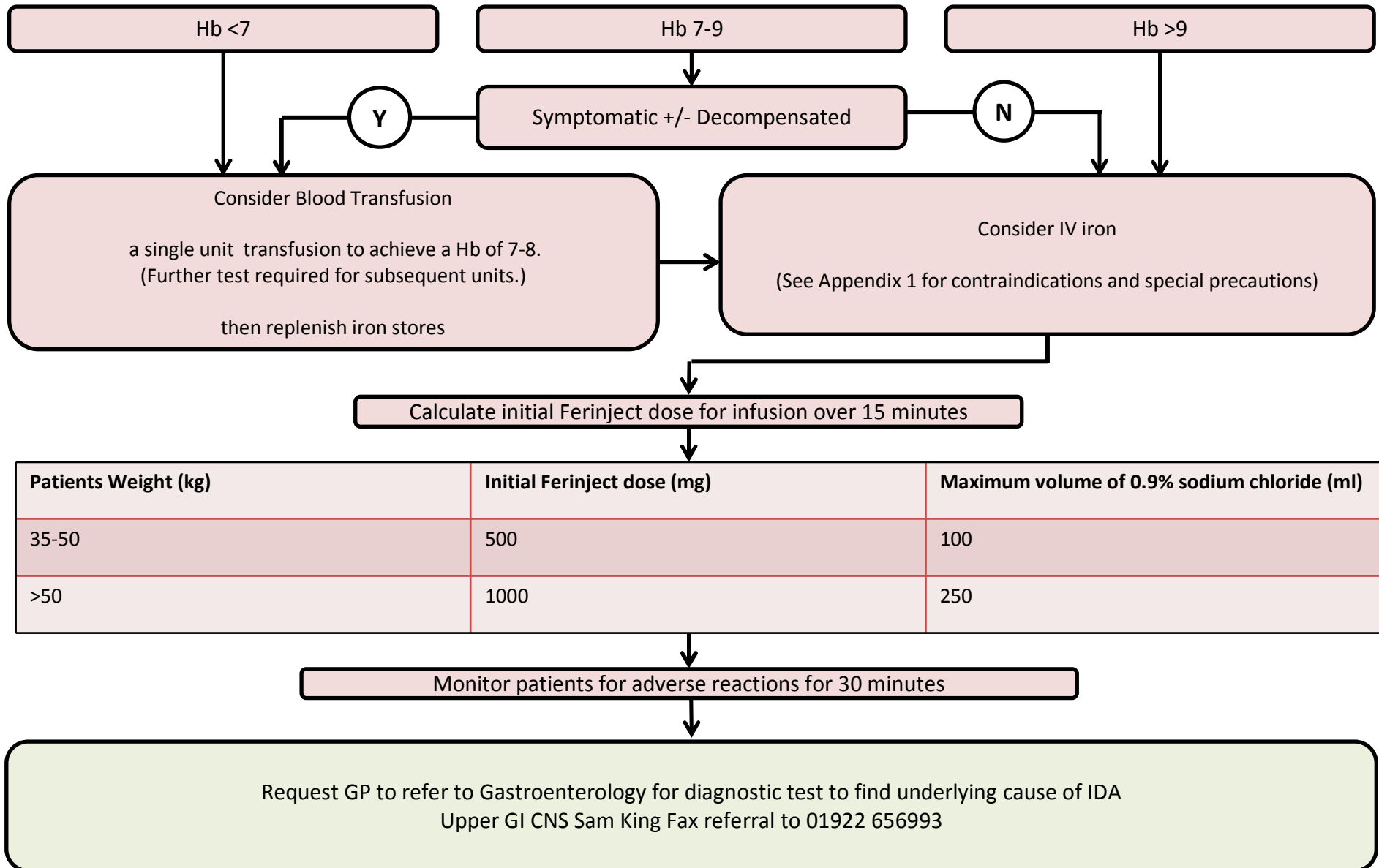
Elective -

We can improve access to IV iron/Oral Iron to preoperative patients.

Pathway

Emergency Iron Deficiency Anaemia Pathway





Patients Weight (kg)	Initial Ferinject dose (mg)	Maximum volume of 0.9% sodium chloride (ml)
35-50	500	100
>50	1000	250

On a lighter note!





**Thank You
For Your**

Attention

**Any
Questions?**

Can Iron be Bad?

Carcinogen or not: Iron in the circulation

No effect of i.v. iron on 3-year progression-free survival in anemic patients with lymphoid malignancies

In CRC mice - No influence on intestinal tumorigenesis, parenteral iron did not promote tumour formation,

Parenteral iron replenished splenic iron and significantly reduced inflammation in the colon without increasing hyperplastic lesions

iron s.c. in APC knockout CRC models did not promote intestinal tumorigenesis.

Carcinogen or not: Iron from the gut?

Murine CRC models – increased tumourigenesis in dietary iron

Gut iron chelators – reduce proliferation and cell cycle in vitro

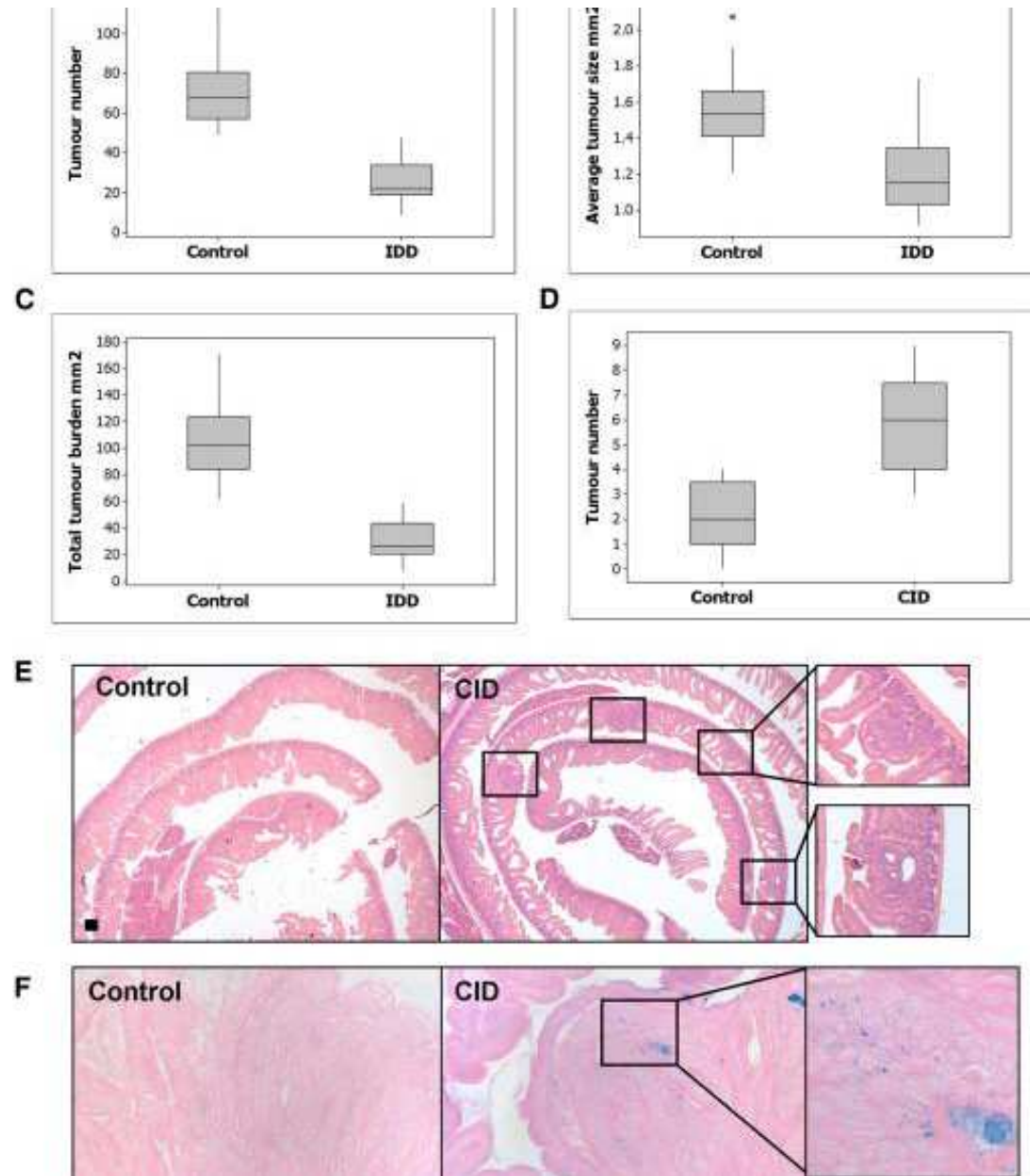
But variable effects in vivo – perhaps due to host toxicity

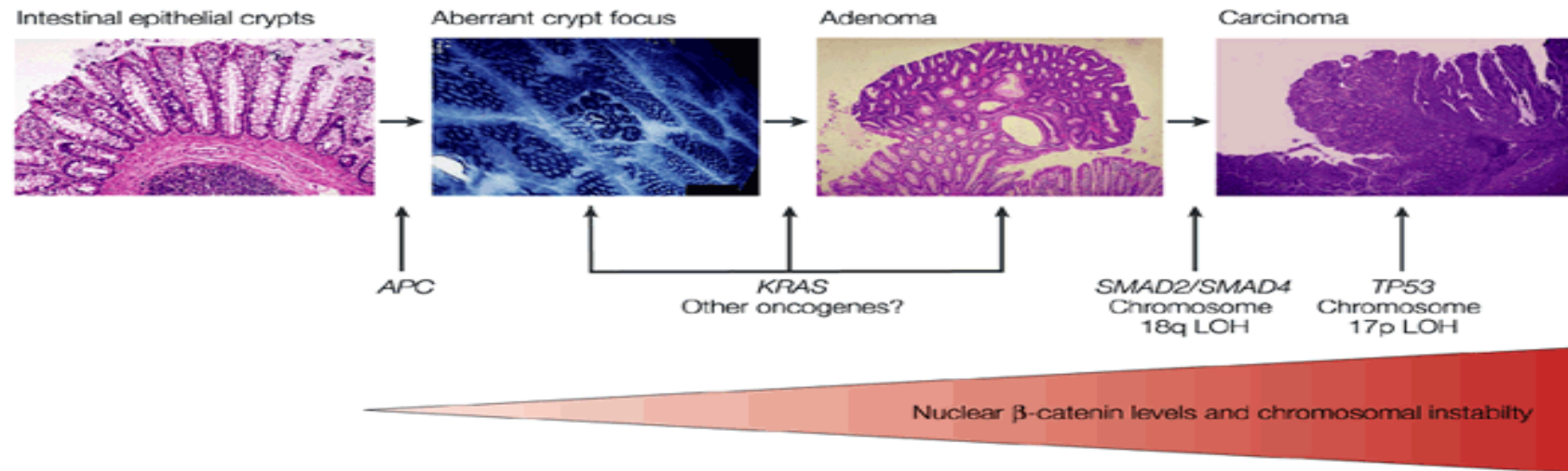
So is Iron Bad?

Iron may be bad if delivered to the gut

Higher effect in vitro seen in genetically predisposed

IV iron has no effect





Nature Reviews | Cancer

B-catenin/TCF binding generates multiple oncogenes via the activation of Wnt-signalling
 APC mutations common in sporadic and familial CRC