



Vitamin D and Fracture risk prevention

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Declarations

- No pharmaceutical funding support for this talk
- In last five years received honoraria, travel and subsistence expenses from:
 - Proctor and Gamble, Servier, Eli Lilly, Roche and Novartis

Where are we now?

- Vitamin D physiology
- Disease associations
- Replacing vitamin D
- Fracture risk prevention

Vitamin D status is important


National Institute for
Health and Clinical Excellence

Issue date: October 2008

Review date: July 2010

**Alendronate, etidronate,
risedronate, raloxifene, strontium
ranelate and teriparatide for the
secondary prevention of
osteoporotic fragility fractures
in postmenopausal women**

Includes a review of NICE technology
appraisal guidance 87, which covered
alendronate, etidronate, risedronate,
raloxifene and teriparatide

NICE technology appraisal guidance 161

This guidance assumes that women who receive treatment have an adequate calcium intake and are vitamin D replete. Unless clinicians are confident that women who receive treatment meet these criteria, calcium and/or vitamin D supplementation should be considered.

Sunshine vitamin??



Olu Deniz Lagoon



The past

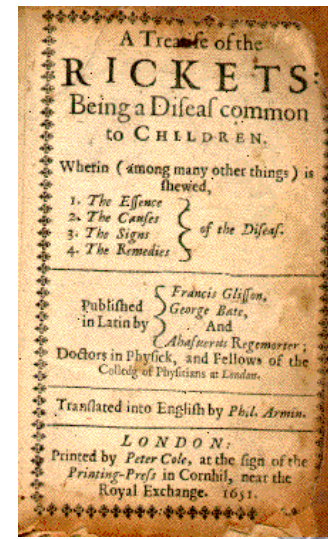
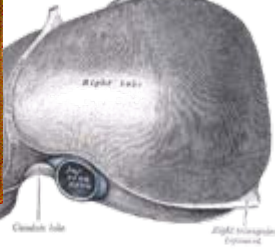
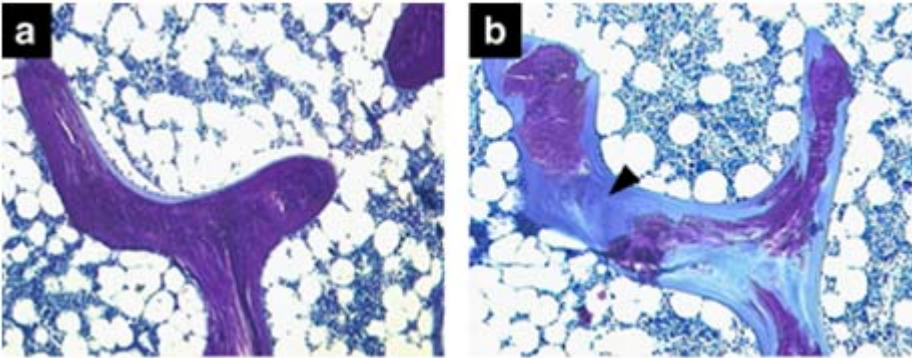


Figure 1 Francis Glisson, 1597-1677. Portrait in the Royal College of Physicians, London.



- First recognized in 1650 by Frances Glisson

1885 bone histology by Pommer



1919 Artificial UV cure
Huldschinsky



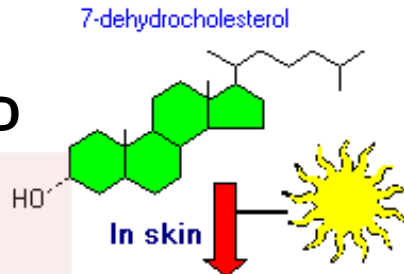
1918 Cod liver oil by Mellenby



Cholecalciferol (D₃)

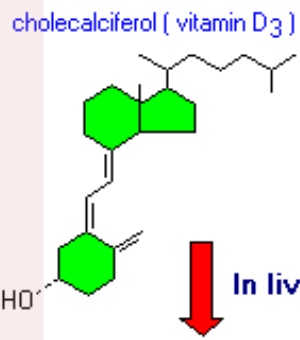


Provitamin D

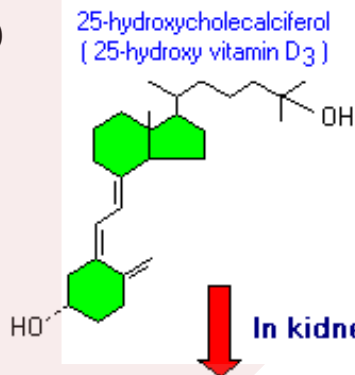


UV 290 – 315 nm (297 peak)
 Converts provitamin D to previtamin D
 Warmth converts previtamin D to cholecalciferol

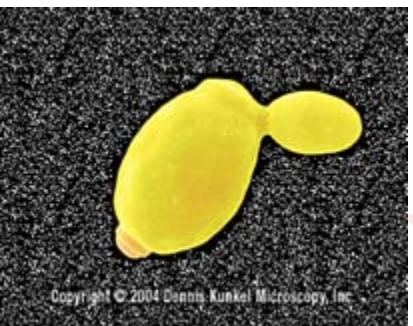
vitamin D



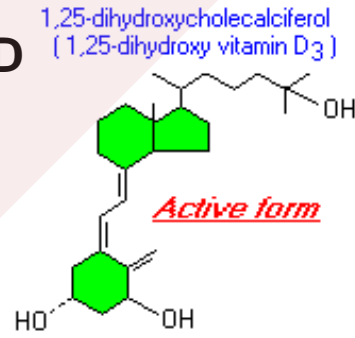
25 vitamin D



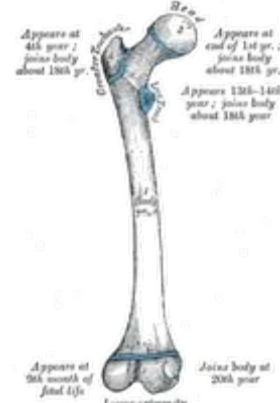
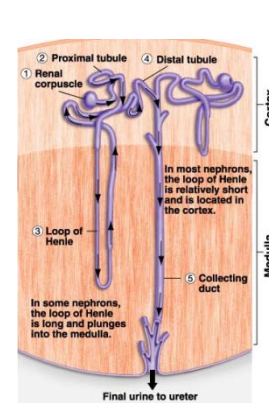
Ergocalciferol (D₂)



1,25 vitamin D



Action



The emerging roles for 25(OH)-vitamin D

Calcium/
phosphate
balance

Muscle

Bone metabolism

Glucose
control/
obesity

25(OH)-
Vitamin D

Osteoarthritis

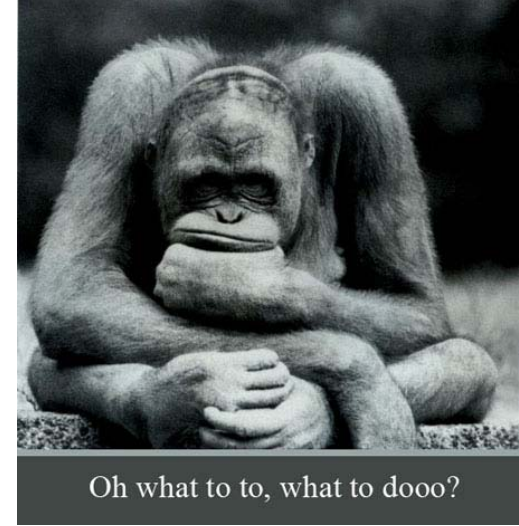
Immune
function

Oncology

Atherosclerosis and
heart failure

Vitamin D units

- Ng/ml
 - Nmol/L
 - IU....
-
- $1 \text{ ng/ml} = 2.5 \text{ nM}$ & $10 \text{ mcg} = 400 \text{ IU}$
 - $< 25 \text{ nM} = \text{severe deficiency}$
 - $25 - 50 \text{ nM} = \text{deficiency}$



Osteomalacia symptoms

- variable
- proximal myopathy, hypotonia
- bone tender and pain
- bowing
- fracture (groin pain)

Vitamin D deficiency predicts future hip fracture

800 women from WHI (7.1yr)

1665 men from MrOS (5.3yr)

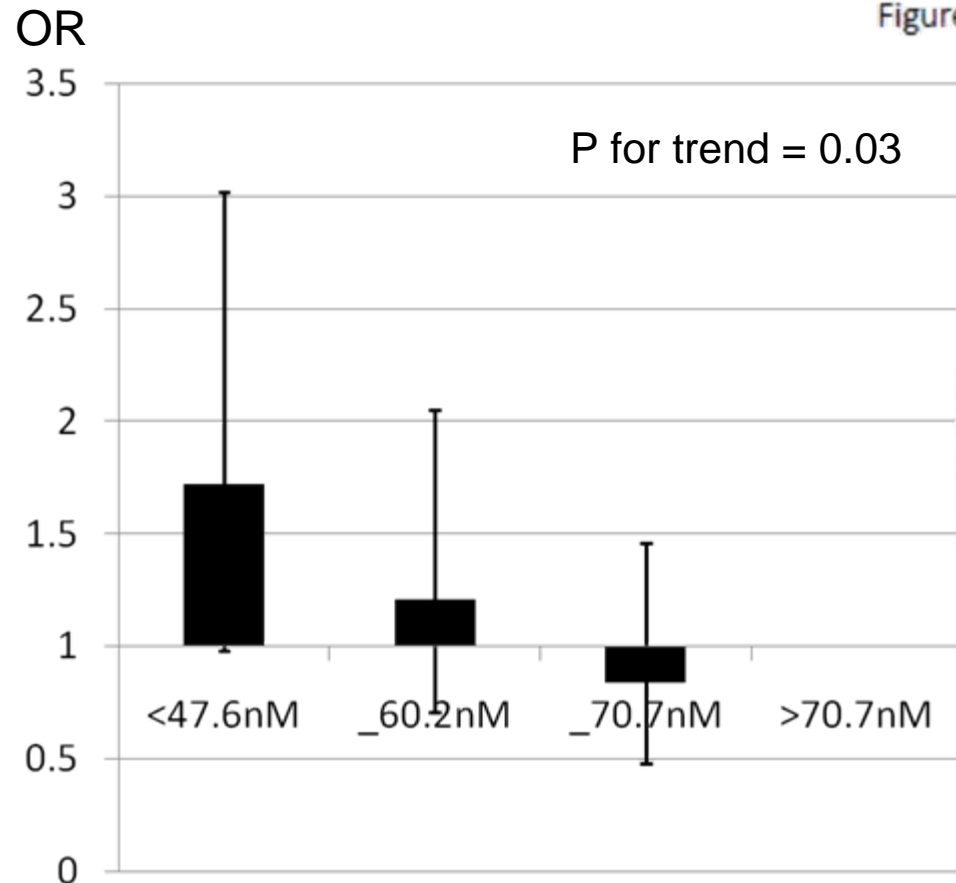
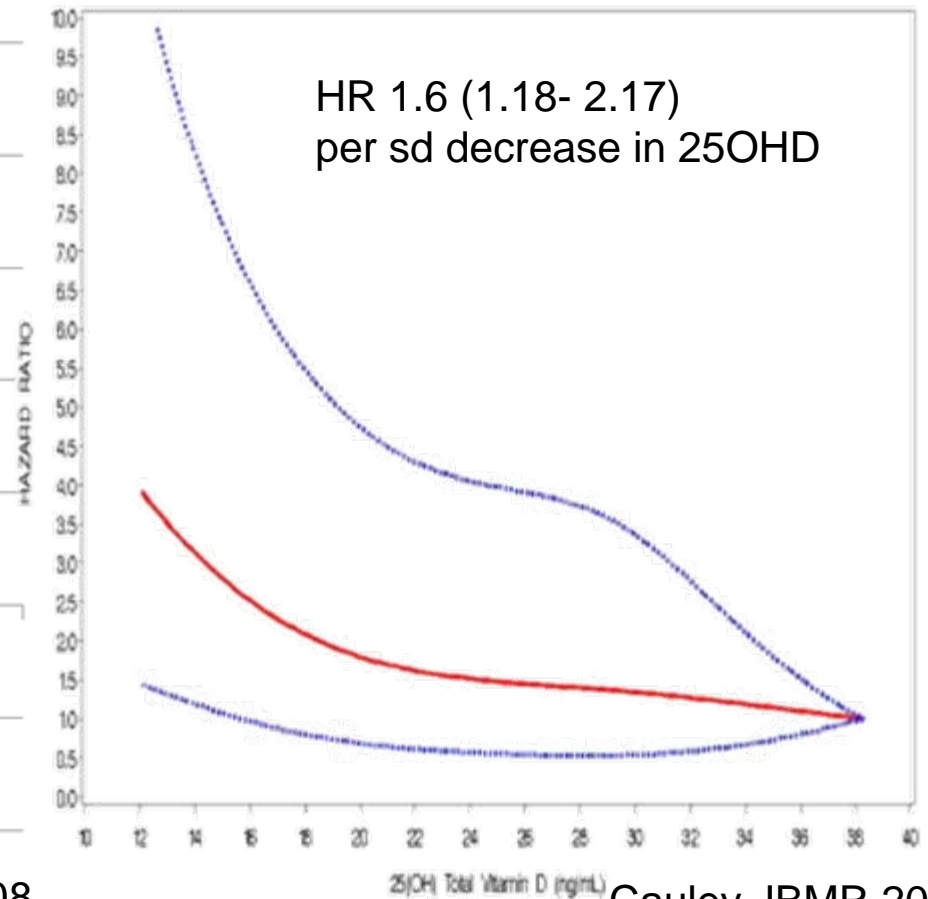


Figure 2

Restricted Cubic Spline Plots of Hazard Ratios of Hip fracture with 25(OH) Total Vitamin D

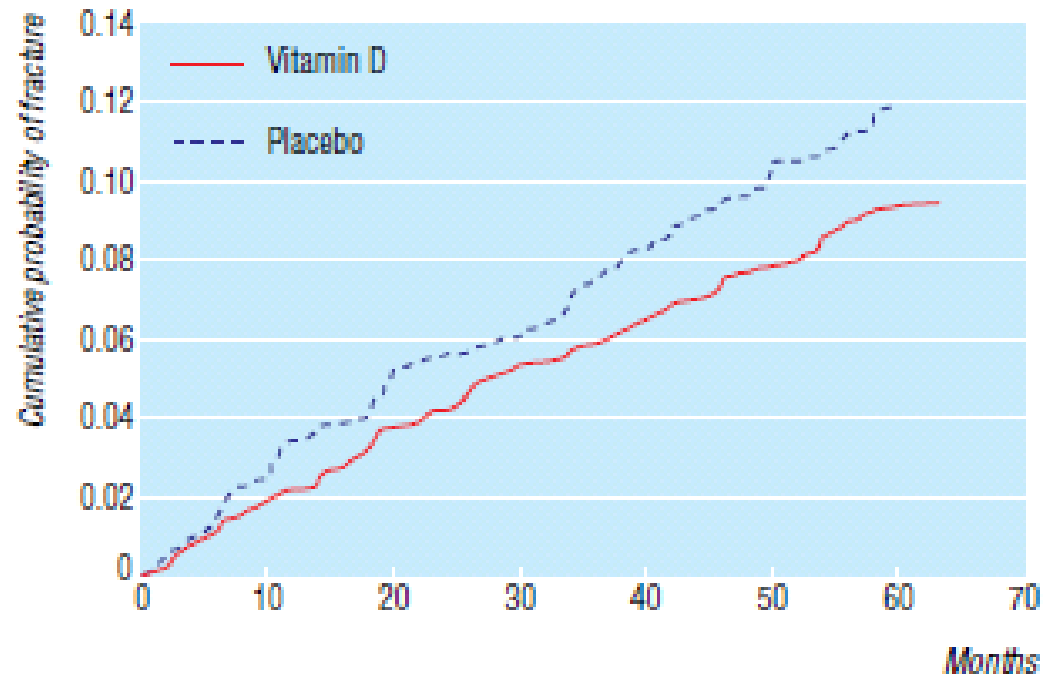


Cauley AIM 2008

Cauley JBMR 2009

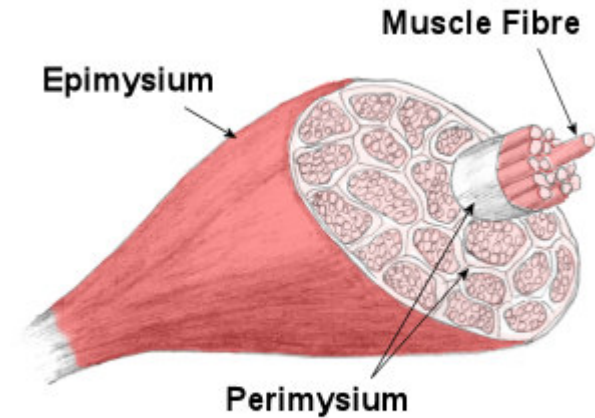
Vitamin D prevents hip fracture

- 100,000 IU D3 4mthly
- British Doctors study
- Ipswich GP practice
- 5 yr Postal study
- 74.3 nM vs 53.4 nM



Vitamin D and falls

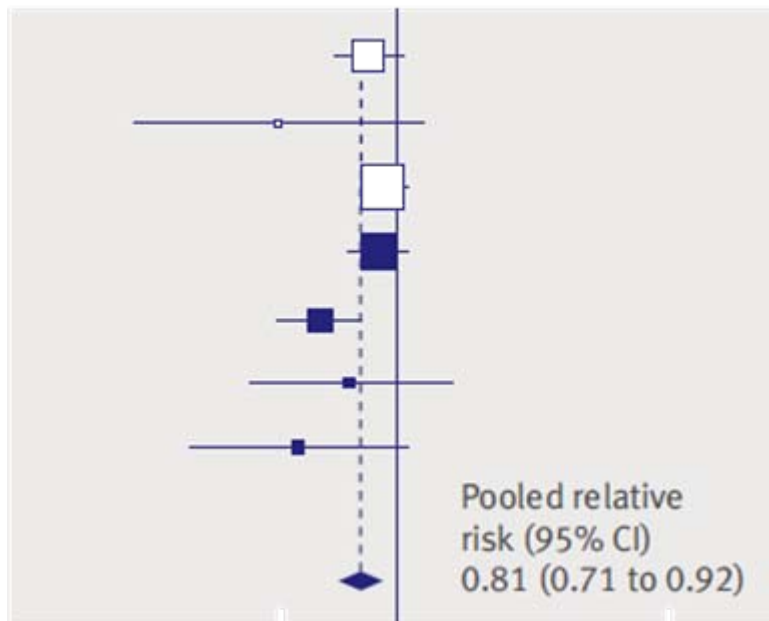
- Store for 25OHD
- VDR – calcium/ anabolic/ fibre type effects



High dose vitamin D

Prince et al^{w3}
 Broe et al^{w1}
 Flicker et al^{w4}
 Bischoff-Ferrari et al^{w2}
 Pfeifer et al^{w5}
 Bischoff et al^{w6}
 Pfeifer et al^{w7}
 Combined

Relative risk (95% CI)



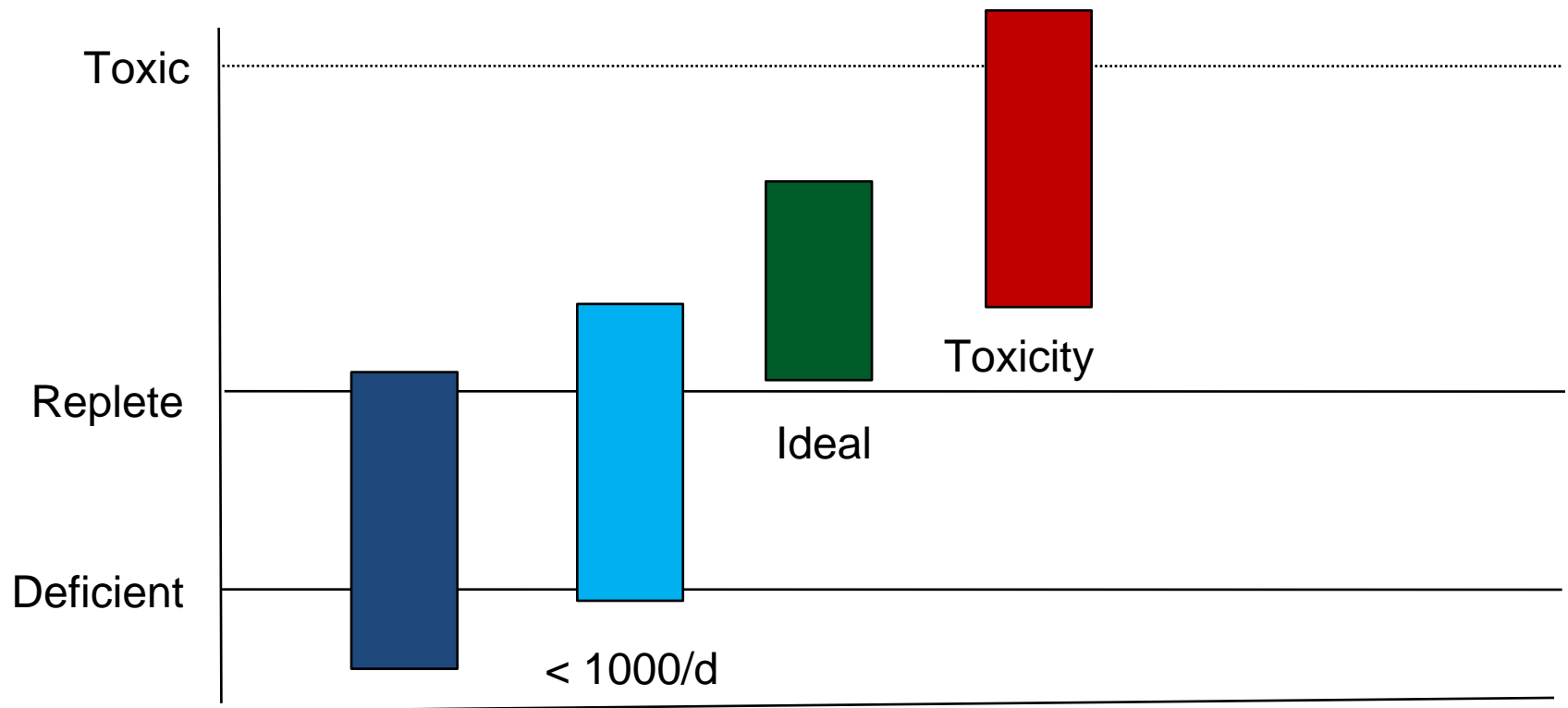
High dose = 700 -1000 IU /d
 < 31,000 IU / mth

No effect in low dose < 600 IU/d
 < 18,600 IU/ mth

Mechanism of action



Effect of daily vitamin D replacement



Vitamin D toxicity – fiction

Daily Mail, Tuesday, September 15, 2009

strokes. Some studies suggest it helps with brain function.

SYMPTOMS OF DEFICIENCY: You can't tell. But if you are not eating the recommended minimum of two portions of oily fish every week, you could probably benefit from taking a supplement.

SOURCES: Salmon, mackerel, sardines and fresh tuna. Look for good quality supplements — check the labels for those with highest levels of DHA or EPA.

SUPPLEMENT RISKS: None known.

■ VITAMIN D

WHAT DOES IT DO? Many functions, including calcium absorption, bone health and immune strength. Also believed to protect against certain cancers, auto-immune diseases and cardiovascular diseases.

SYMPTOMS OF DEFICIENCY: Increased risk of cardiovascular disease, and also falls and fractures due to weak bones.

SOURCES: Ninety per cent of our vitamin D is made by our bodies from sunlight. But the light in the UK is only strong enough from April to September each year, leaving many of us depleted in the winter.

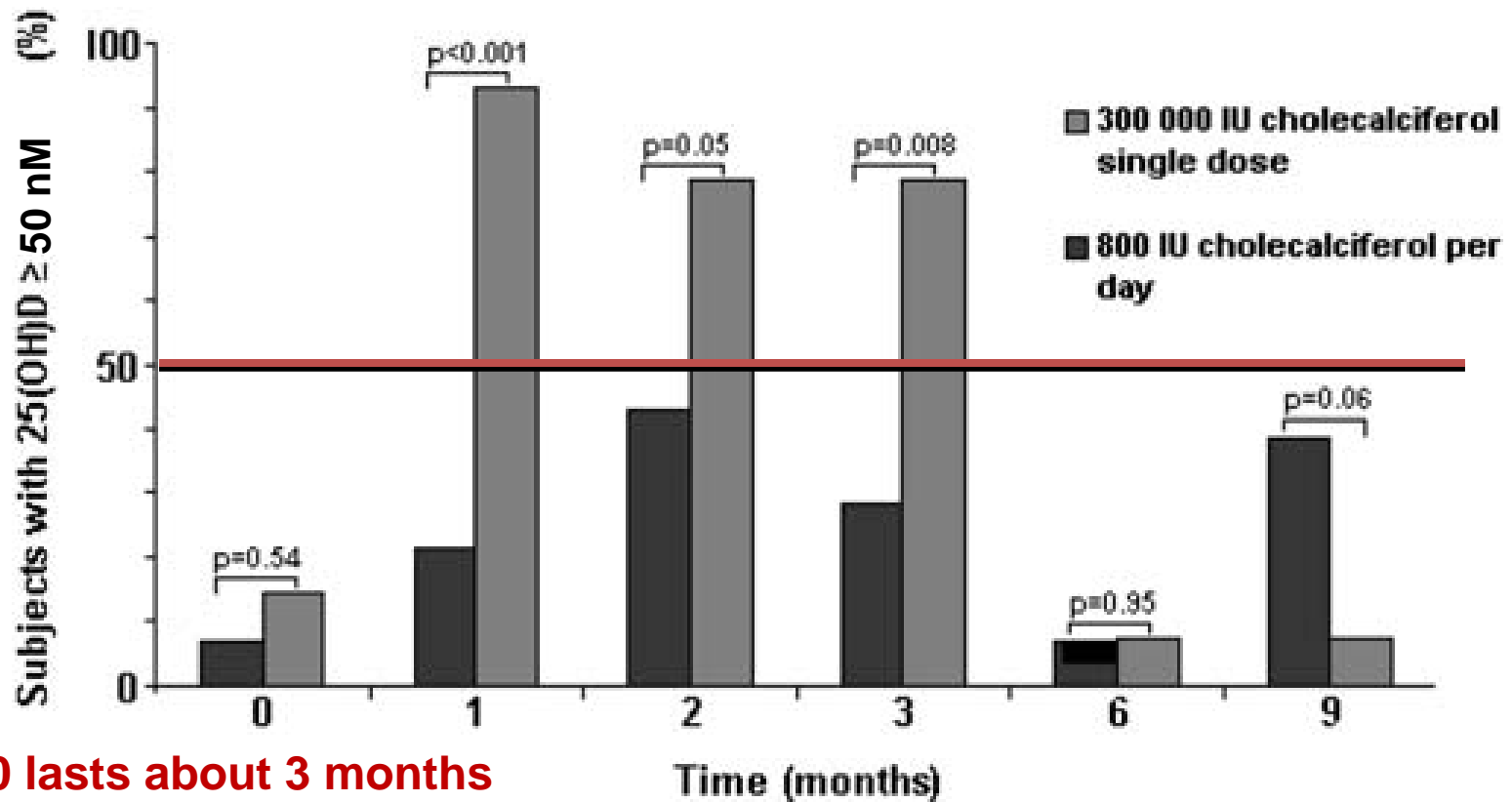
SUPPLEMENT RISKS: Vitamin D is stored in the fat rather than being flushed out in the urine like vitamin C, so taking too much over a short space of time (more than 400IU per day) can be lethal.

SUPPLEMENT RISKS: Vitamin D is stored in the fat rather than being flushed out in the urine like vitamin C, so taking too much over a short space of time (more than 400IU per day) can be lethal.

Vitamin D Toxicity – fact





- Hypercalcaemia (> 2.75 mM)
- Hypercalcuria (> 10 mmol or mM: Uca/Ucr >1)
- Renal stones WHI 1g + 400 IU D
 - 5.6 events per 10,000 years of treatment (OR 1.17)
- Support by recent Cochrane review
- Extra skeletal toxicity?

How much: 300,000 vs 800 IU per day



N= 26 > 65yrs with PTH > 48pg/ml

Treatment principles

- Ergo- vs chole- calciferol  Cholecalciferol lasts longer
- IM vs po administration  Po better absorbed
- Daily vs intermittent dosing  Intermittent better compliance
- Co-administration with Calcium?  Separate as calcium troublesome to take

How much does it cost?

AdCal D3 (600mg Ca/400iu D3); £52/ yr

Calcichew D3 forte (500mg Ca/ 400iu D3): £55/ yr

Calcit D3 (500mg Ca/ 440iu D3): £105/ yr

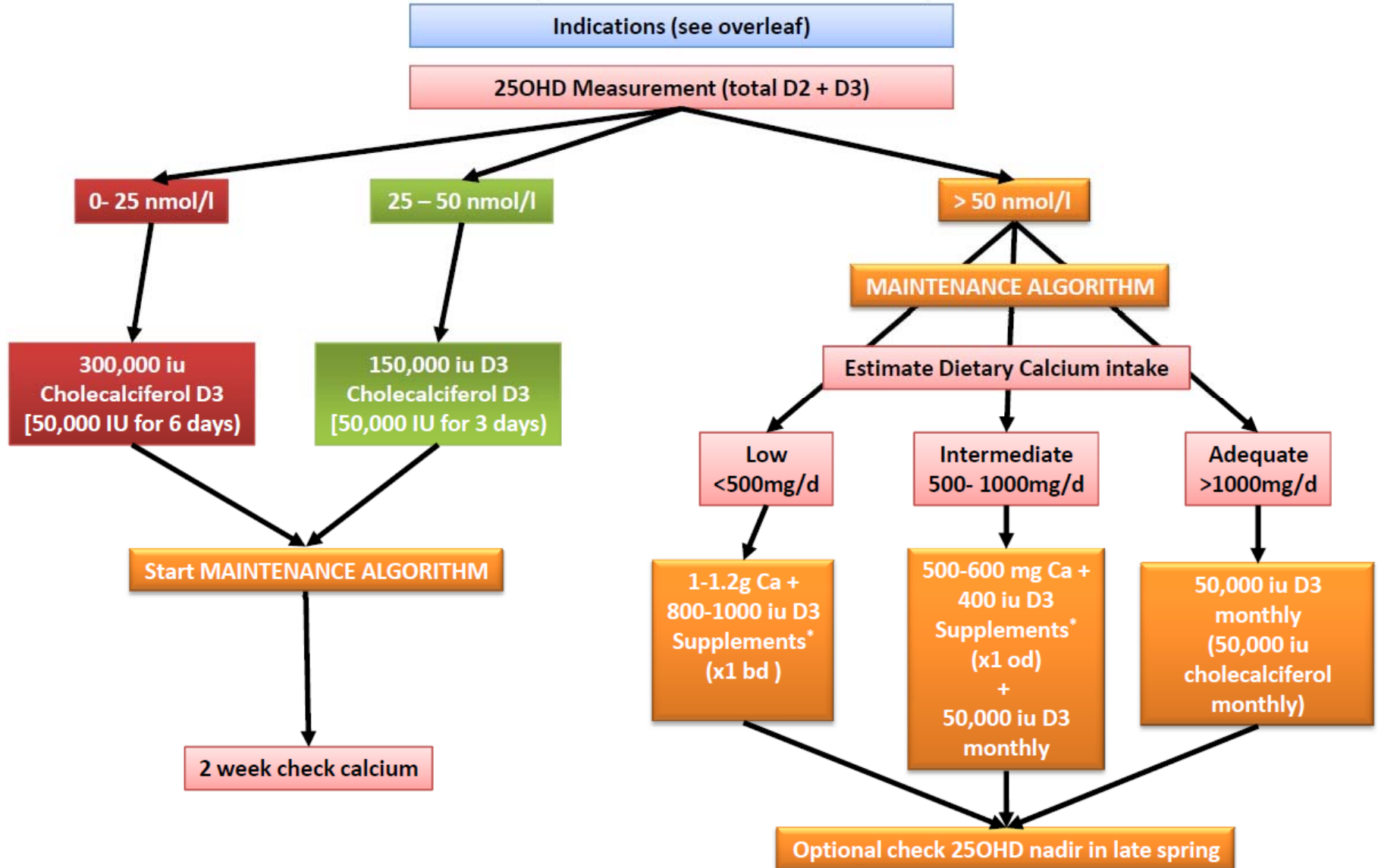
Calfovite D3 (1.2g/ 800iu D3): £55/ yr

Calcium and Ergot (450mg/ 400 iu D2): £37/ yr

Oxford solution...

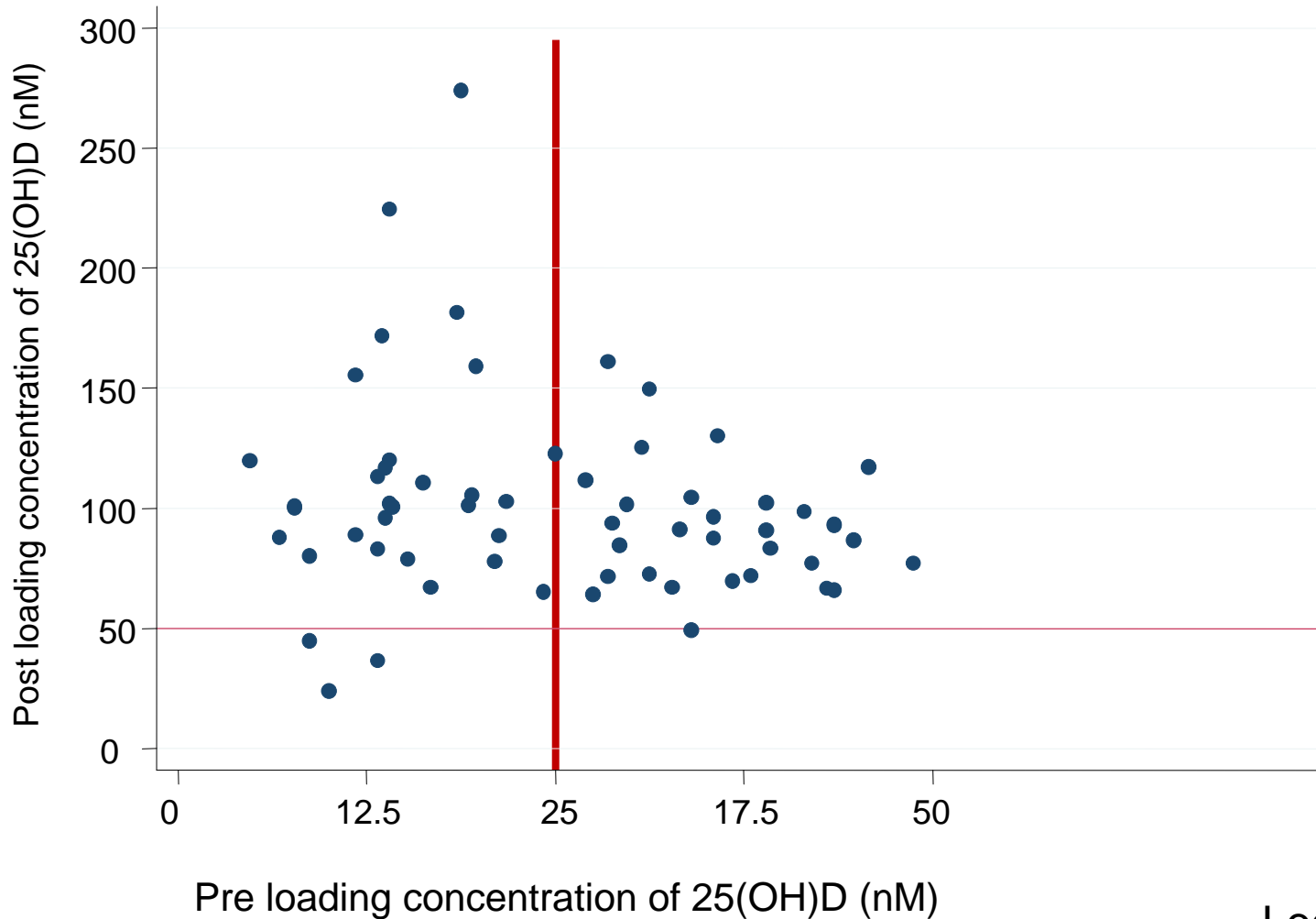
- IDIS Dekristol 20,000 IU D3 23p each
- **Biotech 50,000 IU D3 18.5 p each**
 - **£2.22 / yr for maintenance and £1.11 for loading**
 - Unlicensed in UK
 - FDA approval for over the counter use in USA
 - MHRA approval for import and use in the UK
- Shared guidance for adverse event/ efficacy monitoring...

Oxfordshire Shared guidelines on the management of Vitamin D deficiency in patients with normal/low serum calcium and eGFR > 35 ml/min



Does it work?

Effect of High dose oral loading of 25(OH)D



Is it safe?

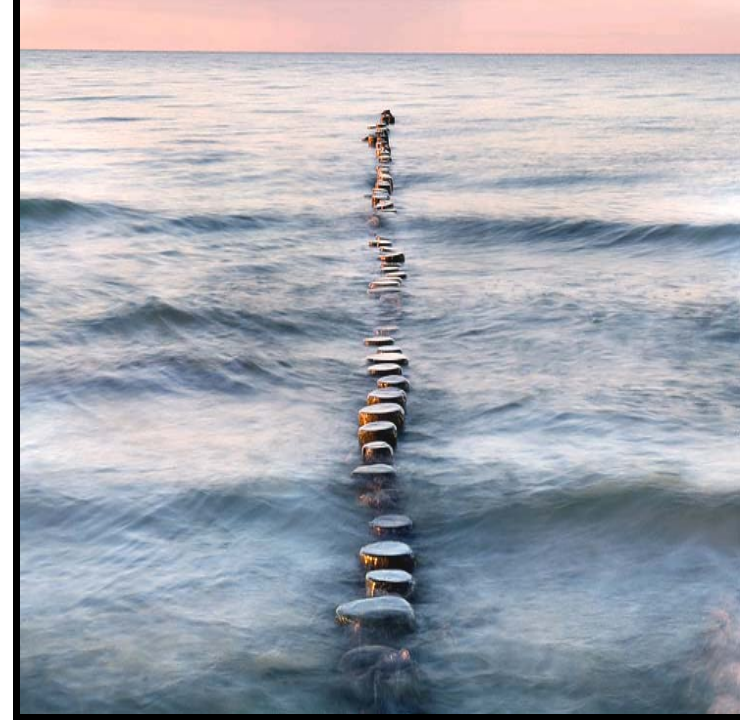
Preloading Deficiency:	Frequency	Post Loading			
		25OHD (IQR)	% replete ¹	Mean Ca ²⁺	Hypercalcaemia (%)
Moderate (10-20 ng/ml)	44.8%	36.3 (28.7, 40.9)	90.1%	2.37 (0.1)	2% (1) ²
Severe (<10ng/ml)	55.2%	40.4 (32.6, 47.9)	96.8%	2.35 (0.08)	0 %

¹Of the 5 patients who were not replete on their post loading 25OHD check, 3 had dates on their blood tests indicating that they had it done before loading and 1 had rise in D from 3.5 to 17.9 ng/ml.

²Already identified with primary hyperparathyroidism (Ca(adj) 2.64 mM)

Oxford journey

- Jun 2008 Guidance produced
- Nov 2008 ORH pharmacy approval
- Mar 2009 MAC Approval – Black light
- May 2009 MHRA import approval
- Aug 2009 MAC Approval – Red light
- May 2009 OxPF applied– needs PH review first
- Nov 2009 OxPF presentation...needs PH review



Summary

- Vitamin D deficiency is common
- Associated with many diseases
- Test for it: 1) OP 2) fallers 3) ethnic minority + symptoms
- High dose therapy is key but supply issues
- Treatment not OxPF yet...

Quantum Specials (01207 279400) or Specials Lab (0800 028 4925)

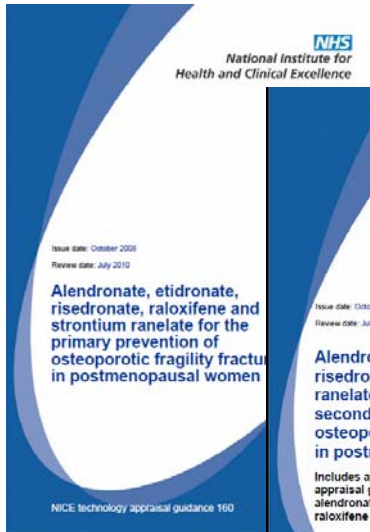


Fascinating
is a word I use for the
unexpected.
In this case,
I should think "*interesting*"
would suffice

Preventing the first and second fragility fracture

- Case finding
- Assessment
- Treatment pathway

Guidance



FRAX™ WHO Fracture Risk Assessment

HOME	CALCULATION TOOL	PAPER CHARTS
<p>Welcome</p> <p>The FRAX™ integrate the</p> <p>The FRAX™ Australia. In versions, ba</p> <p>The FRAX™ probability of</p> <p>This is a beta version</p>	China	
	France	
	Italy	
	Japan	
	Spain	
	Sweden	
	Turkey	
	UK	
	US (Caucasian)	
	US (Black)	
US (Hispanic)		
US (Asian)		

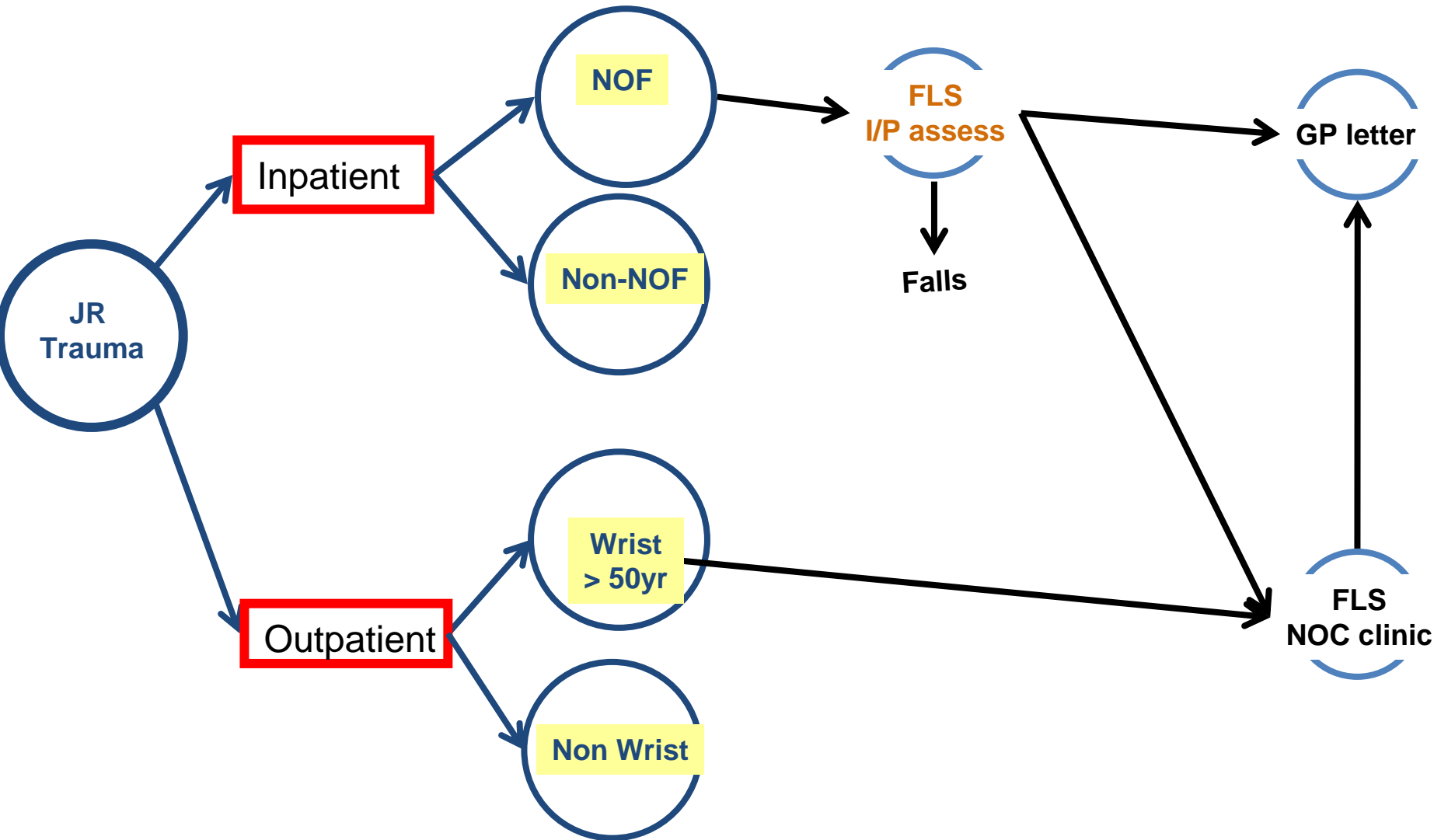
ed by WHO to evaluate clinical risk factors

nogg NATIONAL OSTEOPOROSIS GUIDELINE GROUP

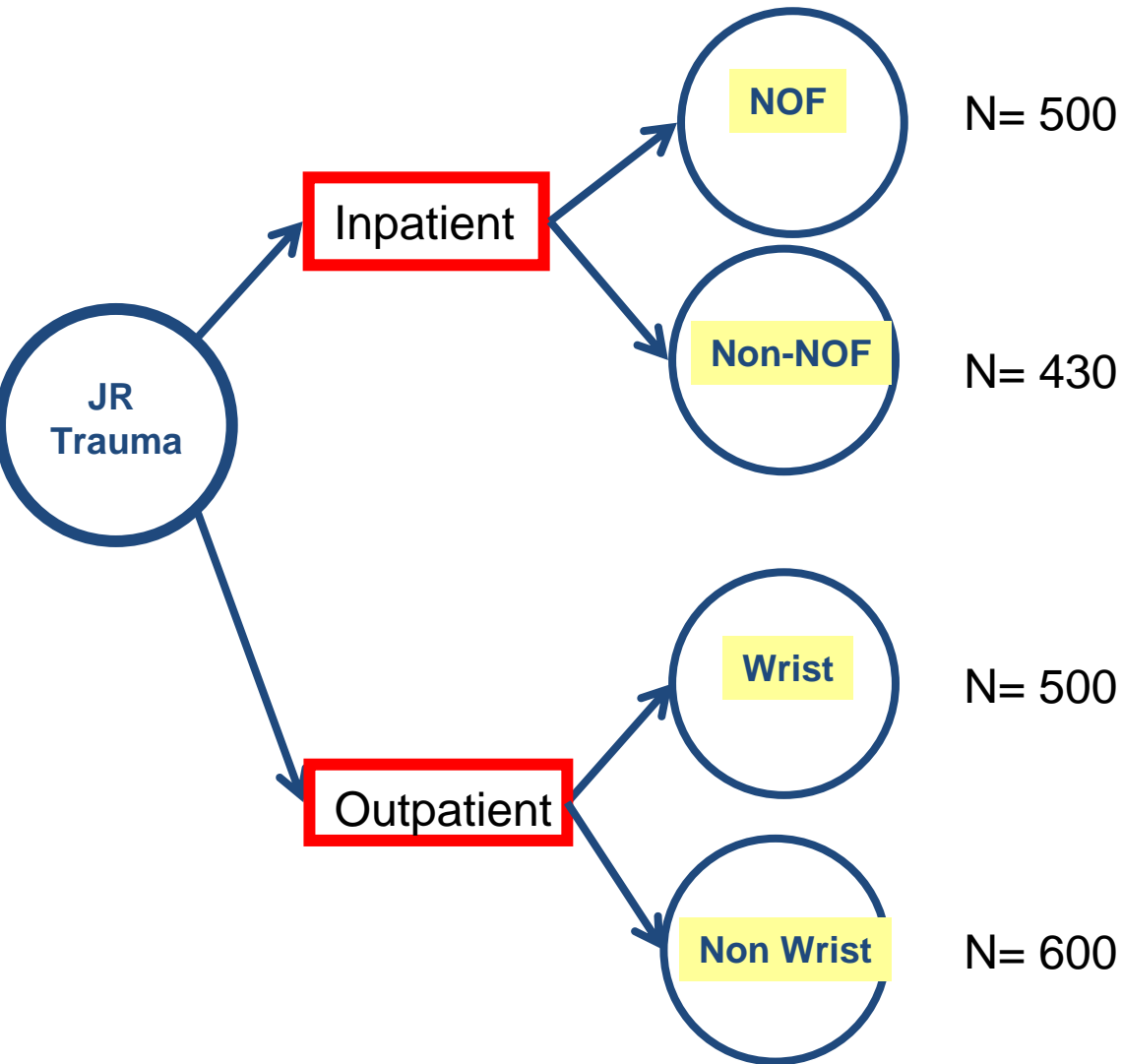
Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK

Developed by J Compston, A Cooper, C Cooper, R Francis, JN Kanis, D Mansi, EJ McCloskey, GM Peck, P Selby and M Wilkins, on behalf of the National Osteoporosis Guideline Group (NOGG)

Current service provision: JR



How many patients?



Current service provision: Horton



NOTHING.....

Equity of health care across
Oxfordshire...
South Central?

A new imperative for change...



Falls and fractures

Developing a local joint strategic needs assessment

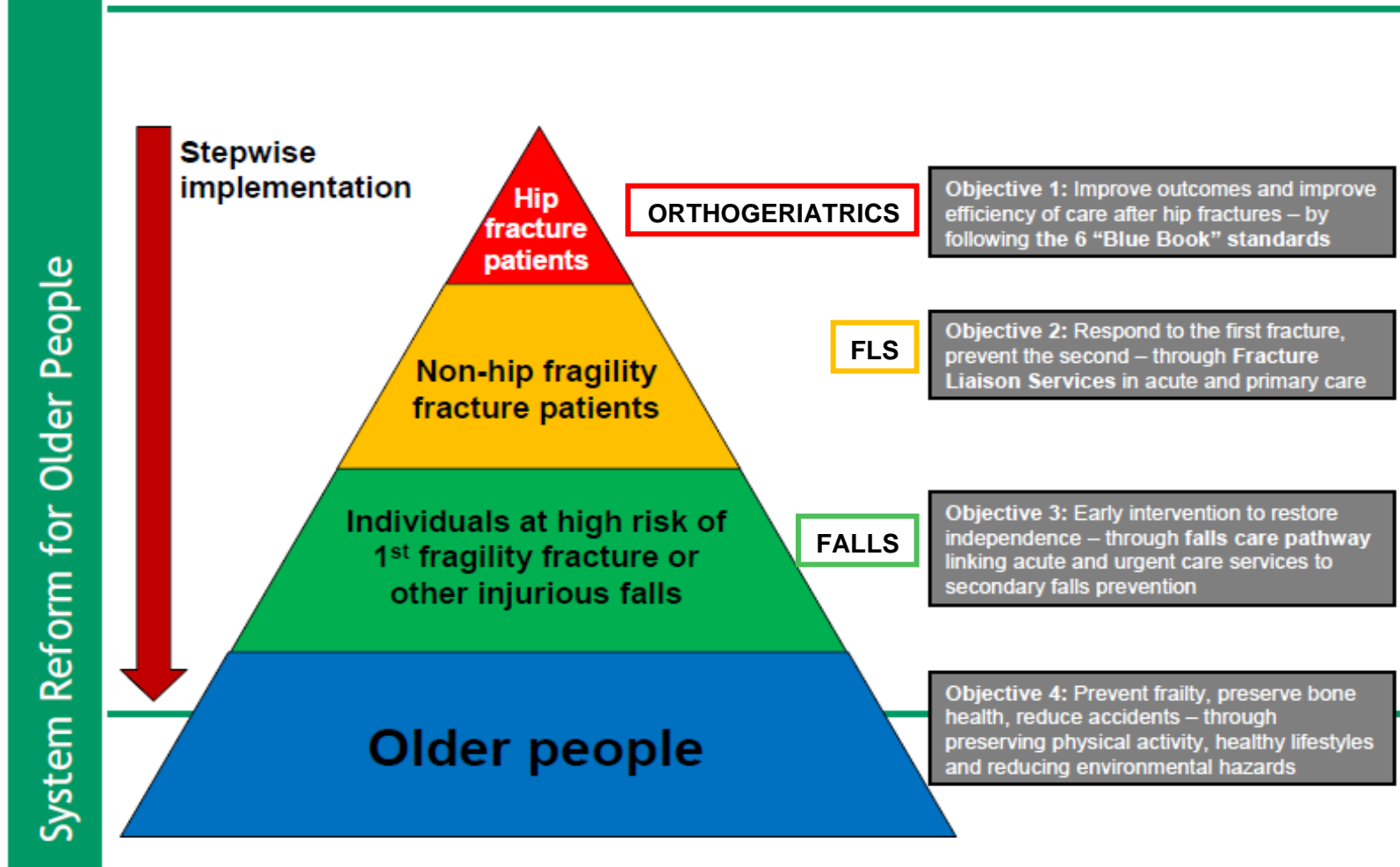


“Get it right the first time”

“After the first fracture, act to prevent the second”

DoH Falls and Fracture Commissioning Toolkit: July 2009

Falls and fracture care and prevention A road map for a systematic approach



The effect of various interventions on 2,660 hip fractures averted by implementation of the DoH toolkit

Intervention	hip fracture averted	% of total
FLS	1,800	68%
Primary	370	14%
Care Homes	480	18%
Exercise	10	0.4%



Fracture
Reduction
in
South
Central
policy



H
O
W
?

- Berkshire
- Buckinghamshire
- Oxfordshire
- Hampshire
- Isle of Wight



**“Equitable and effective health care provision:
After the first fracture, act to prevent the second”**



Identify local key players

Survey current practice

Establish regional Joint needs Assessment

Develop service specification for case finding,
assessment and treatment

Generate local business case



Identify local key players ✓

Survey current practice ✓

Establish regional Joint needs Assessment ✓

Develop service specification for case finding,
assessment and treatment (✓ drafted)

Generate local business case



Results of survey: Doh objectives by site

Region	Site	Population served	Obj. 1		Objective 2			Obj. 4	
			Orthogeriatrician	NHFD	Fracture Liaison Service (capture/ assessment/ treatment/ monitoring)				Dedicated Bone clinic
					Inpatient	OPD	Primary care		
Berkshire	Reading	550,000	✓	?	x	✓	x	2/ mth	✓
	Wexham	450,000	(✓ 2010)	x	x	x	x	0/ mth	✓
Buckinghamshire	Milton Keynes	280,000	✓	✓	x	x	x	1.5/mth	✓
	Stoke Mandeville	500,000	✓	✓	(✓) pilot	x	x	2/ mth	✓
Hampshire	Basingstoke	280,000	✓	✓	x	x	x	0 / mth	✓
	Portsmouth	600,000	✓	✓	x	x	x	0 / mth	✓
	Southampton	600,000	✓	✓	x	x	x	4/ mth	✓
	Winchester	200,000	✓	✓	x	x	x	0/ mth	✓
Isle of Wight	26/10/09	140,000	✓	(✓)	✓	x	x	8/ mth	✓
Oxfordshire	John Radcliffe	500,000	(✓) part-time	✓	(✓) only NOFs	(✓) only wrists	x	8/ mth	✓
	Horton	400,000	x	x	x	x	x	0/ mth	✓



Good provision of falls, moderately good coverage with orthogeriatrics

Region	Site	Population served	Obj. 1		Objective 2			Obj. 4	
			Orthogeriatrician	NHFD	Fracture Liaison Service (capture/ assessment/ treatment/ monitoring)			Dedicated Bone clinic	Falls
					Inpatient	OPD	Primary care		
Berkshire	Reading	550,000	✓	?	x	✓	x	2/ mth	✓
	Wexham	450,000	(✓ 2010)	x	x	x	x	0/ mth	✓
Buckinghamshire	Milton Keynes	280,000	✓	✓	x	x	x	1.5/mth	✓
	Stoke Mandeville	500,000	✓	✓	(✓) pilot	x	x	2/ mth	✓
Hampshire	Basingstoke	280,000	✓	✓	x	x	x	0 / mth	✓
	Portsmouth	600,000	✓	✓	x	x	x	0 / mth	✓
	Southampton	600,000	✓	✓	x	x	x	4/ mth	✓
	Winchester	200,000	✓	✓	x	x	x	0/ mth	✓
Isle of Wight	26/10/09	140,000	✓	(✓)	✓	x	x	8/ mth	✓
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	Horton	400,000	x	x	x	x	x	0/ mth	✓



FLS very poor coverage but most effective...

Region	Site	Population served	Obj. 1		Objective 2			Obj. 4	
			Orthogeriatrician	NHFD	Fracture Liaison Service (capture/ assessment/ treatment/ monitoring)				Dedicated Bone clinic
					Inpatient	OPD	Primary care		
Berkshire	Reading	550,000	✓	?	✗	✓	✗	2/ mth	✓
	Wexham	450,000	(✓ 2010)	x	✗	✗	✗	0/ mth	✓
Buckinghamshire	Milton Keynes	280,000	✓	✓	✗	✗	✗	1.5/mth	✓
	Stoke Mandeville	500,000	✓	✓	(✓) pilot	✗	✗	2/ mth	✓
Hampshire	Basingstoke	280,000	✓	✓	✗	✗	✗	0 / mth	✓
	Portsmouth	600,000	✓	✓	✗	✗	✗	0 / mth	✓
	Southampton	600,000	✓	✓	✗	✗	✗	4/ mth	✓
	Winchester	200,000	✓	✓	✗	✗	✗	0/ mth	✓
Isle of Wight	26/10/09	140,000	✓	(✓)	✓	✗	✗	8/ mth	✓
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	Horton	400,000	x	x	✗	✗	✗	0/ mth	✓

An example of collaboration; Service specification

MEDICAL MANAGEMENT OF MEN AND WOMEN OVER 50YRS WHO HAVE SUSTAINED A FRAGILITY FRACTURE

Fragility fracture definition
Fracture site excluding fingers, toes, scaphoid and skull
Fragility = trauma excluding major RTA or fall from more than 10 feet

All patients should be assessed to rule out secondary causes as well as falls risk

BLOOD/ URINE INVESTIGATIONS¹
Bone profile (serum calcium, phosphate, ALP, Albumin)
25OH vitamin D, Renal function,
ALT/ γGT, FBC, ESR, TSH, Coeliac screen

IMAGING INVESTIGATIONS¹
Lumbar spine (L1-L4) + Total hip / femoral neck DXA
(if over 75 years and DXA clinically inappropriate then treat)

Normal
Lowest T score > -1.5

Osteopenia
Lowest T score
-1.5 TO -2.5

Osteoporosis
Lowest T score < -2.5
Or current glucocorticoid use

General guidance
Smoking cessation
Alcohol moderation
Dietary calcium advice

Consider repeat BMD in 3 yrs if osteopenic

Vertebral fracture or
Or Inflammatory disease?

General guidance +
Ensure calcium intake at least 1.0g/d
Ensure circulating 25OH vitamin D ≥20ng/ml

NICE TA 161:
1st line Alendronate 70mg/wk except if significant Upper GI disease

3 months medicine use review: if not adherent consider:
Risedronate 35mg/d
Strontium 2g/d

iv. Zoledronate or Teriparatide therapy require specialist review

Ibandronate use on case by case basis

- If New or Worsening heartburn on bisphosphonate, SWITCH RATHER THAN ADD IN PPI

- Review treatment at 5 years

-if fragility fracture on treatment after one year, check adherence and consider switching.

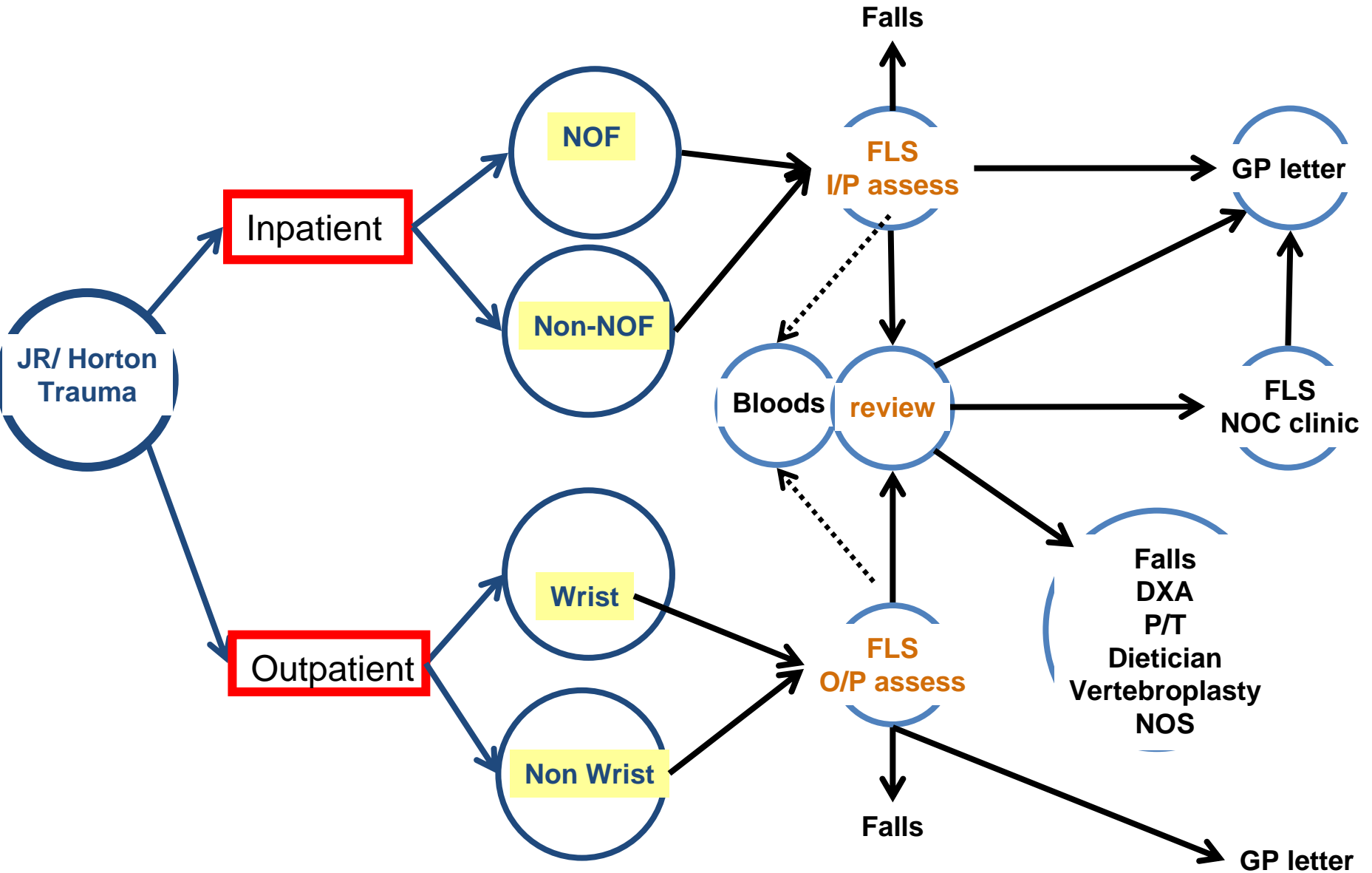
INDICATIONS for Referral to bone clinic:

- Pre-menopausal or men under the age of 60 years presenting with osteoporosis
- Fracture after one year of compliant therapy
- Inability to take or tolerate oral treatments
- Osteoporosis due to complex medical diseases (breast/prostate cancer, kidney disease etc).
- Acute painful vertebral fractures

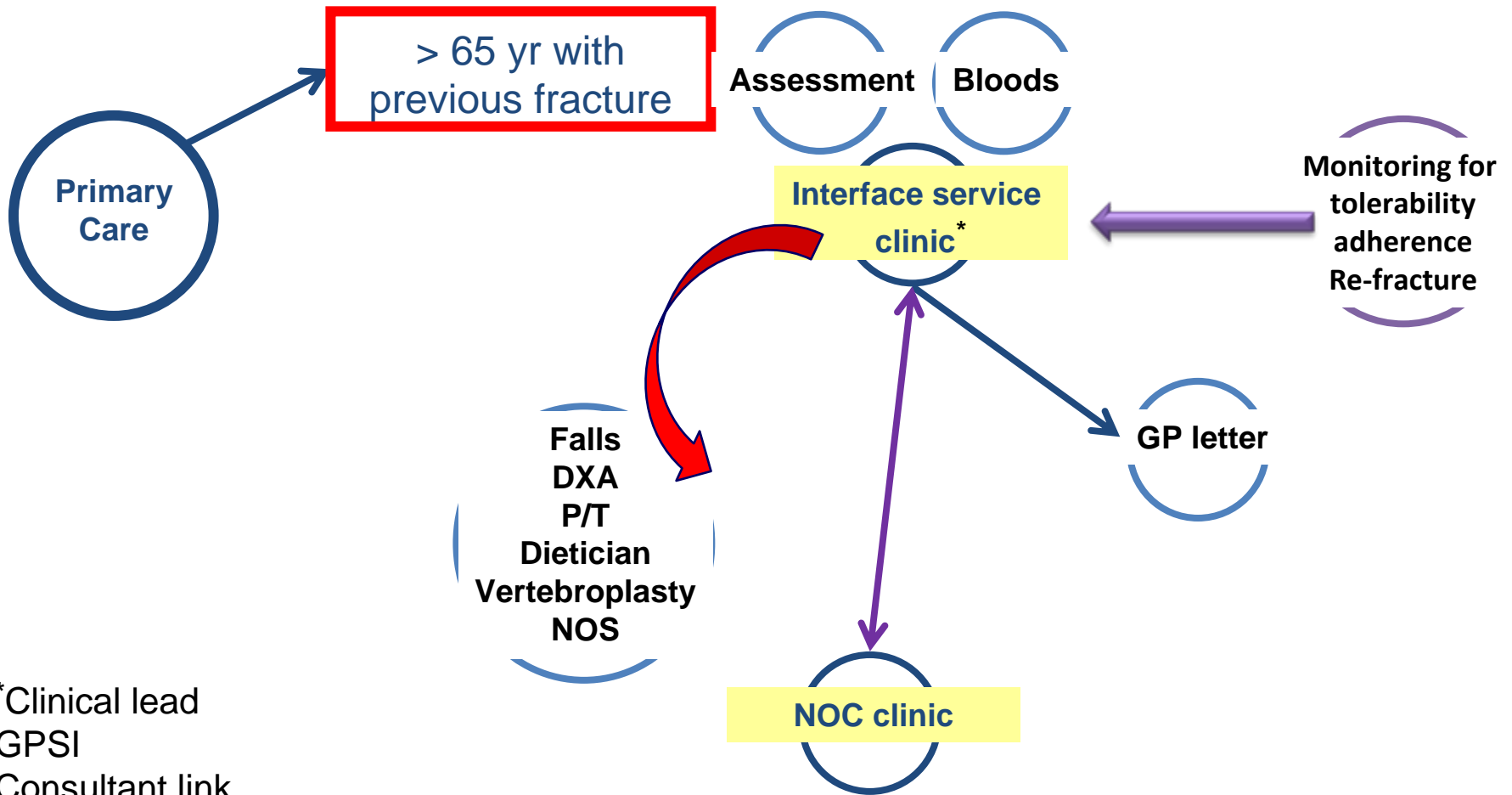
¹Additional Investigations if indicated:

- Serum & urine electrophoretic strip if unexplained high ESR
- PTH, 24 hour urinary calcium/creatinine if hypercalcaemia or renal stones
- Serum testosterone, LH and SHBG
- PSA
- 24 hour urinary cortisol x2 if suspect Cushing's disease
- DXA: Vertebral fracture assessment to be performed if osteopenic

The next step secondary care: Near patient assessment



The next step: Primary care



Monitoring for
tolerability
adherence
Re-fracture

Assessment

Bloods

Interface service
clinic*

GP letter

NOC clinic

> 65 yr with
previous fracture

Primary
Care

Falls
DXA
P/T
Dietician
Vertebroplasty
NOS

- *Clinical lead
- GPSI
- Consultant link
- Fracture liaison practitioner
- Business manager
- Administration



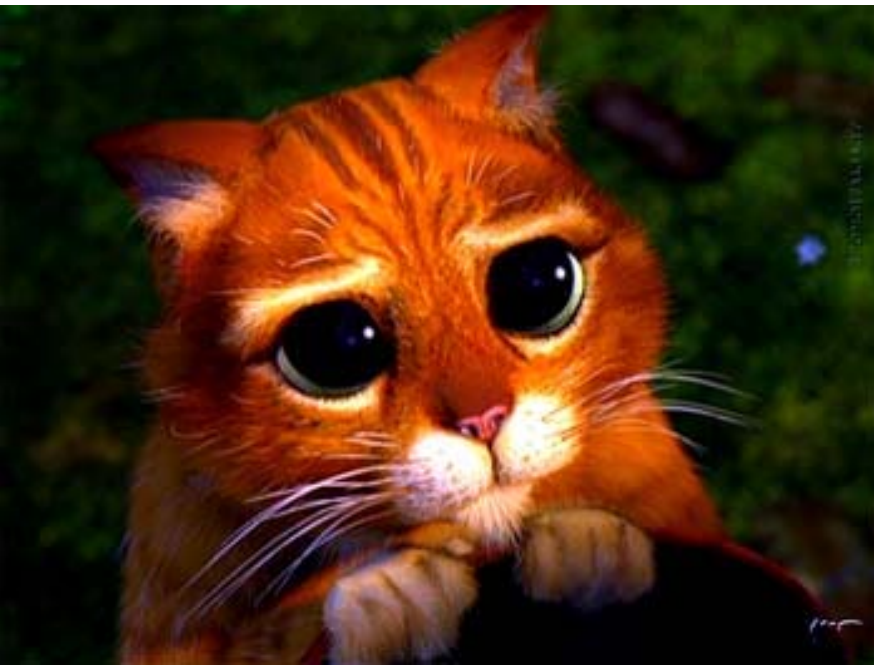
Capture, Assessment & Treatment

We know how to identify patients

We have the drugs to treat patients effectively

Need to implement into our current practice

Time to coordinate action is now





Acknowledgements

John Wass
Keith Willett
Kerri Rance
Rachael Knight
Carol Weeks
Sally Hope

Cyrus Cooper
Nigel Arden

Nuffield **NHS**
Orthopaedic Centre
NHS Trust



UNIVERSITY OF
Southampton



Quantum Specials (01207 279400) or
Specials Lab (0800 028 4925)