Treatment of Osteoporosis: IHFD 6th March 2015

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Vice-President International Society for Clinical Densitometry
Conflicts of Interest

✧ Dr. John Carey has received grants, speaker fees, consulting fees and travel support from the manufacturers of all licensed brand name medications in Ireland and USA including MSD, Eli Lilly, Roche, Proctor and Gamble, Novartis, Amgen and others.

✧ Dr. John Carey’s father was the O.H. physician for M.S.D. Ireland from 1974-2010.
Outline

✦ Background

✦ Treatment

✦ The Care-gap
Osteoporosis is not a silent disease!

“I’ve had 5 children doctor and I’d gladly have 10 more before I’d go through the pain I had with that hip fracture”

Retired Professional, Age 72
Global Incidence of Hip Fractures
Treatment has been shown to:

• Reduces the risk of future fracture
• Reduce morbidity
• Reduce cost of care
• Reduce mortality
Treatment

• Manage co-morbidities

• Fall Reduction

• Nutrition: protein, calcium, vitamin D

• Osteoporosis medication

• Other: hip pads, back-packs, surgery
Who Needs Osteoporosis Treatment?
Postmenopausal women & men ≥ 50 years with:

• A hip or vertebral fracture

• Low bone mass and other risk factors associated with high risk of fracture; e.g. other fracture, glucocorticoids

• T-score < -2.5 at the hip or spine after appropriate evaluation to exclude secondary causes

• Others with Low bone mass and high fracture risk

* Low bone mass = T-score: -1.0 to -2.5 at FN, TH, or spine.

Vitamin D & Calcium Prevent Fractures in Women

Note: 800 IU D3, Mean age 84 years

Mean age 64 years; Vitamin D 400 units
Calcium 100mg/day (>40% on supplements)
1 year Fracture Risk on C+D


% Incidence of New Vertebral Fracture Within 1 Year

Number of Baseline Vertebral Fractures
2011 IOM Report: Calcium and Vitamin D (1258 pages!!)

No evidence for any non-skeletal benefits

Recommend:
600-800 units per day Vitamin D
1000-1300 mg per day Calcium
Last Century.....

• 1977 FDA Approval of Didronel for Paget’s disease of bone and Heterotopic ossification

• 1994 – WHO DXA criteria for Diagnosis
  – Didronel Approved for Rx in Europe,
  – FDA says no but following week approves calcitonin!

• 1995 Fosamax 10mg/day EMA & FDA approval for PMO and PDB.
  – Later GIO, men and weekly dosing
**Approved Osteoporosis Treatments in Ireland**
MIMS Ireland Jan 2012; www.medicines.ie

<table>
<thead>
<tr>
<th></th>
<th>Postmenopausal Osteoporosis</th>
<th>Male Osteoporosis</th>
<th>Glucocorticoid Induced Osteoporosis</th>
<th>Prevention of the Following Fractures</th>
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<tbody>
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<td>Rx</td>
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<td>Tibolone</td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
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<td>-</td>
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<td>Y</td>
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<td>Y</td>
<td>Y</td>
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<tr>
<td>Zoledronate</td>
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<td>Y</td>
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<td>Y</td>
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<tr>
<td>Strontium Ranelate</td>
<td>-</td>
<td>Y</td>
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<td>Denosumab</td>
<td>-</td>
<td>Y</td>
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<td>Y</td>
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<td>Bazedoxifene</td>
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<td>Y</td>
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<td>PTH (1-84)</td>
<td>-</td>
<td>Y</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Teriparatide</td>
<td>-</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
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</table>
Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures

Dennis M Black, Steven R Cummings, David B Karpf, Jane A Cauley, Desmond E Thompson, Michael C Nevitt, Douglas C Bauer, Harry K Genant, William L Haskell, Robert Marcus, Susan M Ott, James C Torner, Sara A Quandt, Theodore F Reiss, Kristine E Ensrud, for the Fracture Intervention Trial Research Group

Summary

Background Previous studies have shown that alendronate can increase bone mineral density (BMD) and prevent radiographically defined (morphometric) vertebral fractures. The Fracture Intervention Trial aimed to investigate the effect of alendronate on the risk of morphometric as well as clinically evident fractures in postmenopausal women with low bone mass.

Methods Women aged 55–81 with low femoral-neck BMD

alendronate versus placebo were 0.49 (0.23–0.99) and 0.52 (0.31–0.87). There was no significant difference between the groups in numbers of adverse experiences, including upper-gastrointestinal disorders.

Interpretation We conclude that among women with low bone mass and existing vertebral fractures, alendronate is well tolerated and substantially reduces the frequency of morphometric and clinical vertebral fractures, as well as other clinical fractures.
Effects of Risedronate Treatment on Vertebral and Nonvertebral Fractures in Women With Postmenopausal Osteoporosis: A Randomized Controlled Trial

Context Risedronate, a potent bisphosphonate, has been shown to be effective in the treatment of Paget disease of bone and other metabolic bone diseases but, to our knowledge, it has not been evaluated in the treatment of established postmenopausal osteoporosis.

Objective To test the efficacy and safety of daily treatment with risedronate to reduce the risk of vertebral and other fractures in postmenopausal women with established osteoporosis.

Significant Reduction (40%) in vertebral and nonvertebral fractures
No difference in adverse events
Effectiveness of bisphosphonates on nonvertebral and hip fractures

Fig. 4 Cumulative incidence of hip fractures in patients treated with alendronate or risedronate for up to 1 year.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>month 3</th>
<th>month 6</th>
<th>month 9</th>
<th>month 12</th>
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<tbody>
<tr>
<td>Alendronate Patients</td>
<td>21615 (0)</td>
<td>21590 (25)</td>
<td>12993 (54)</td>
<td>8677 (69)</td>
<td>5582 (80)</td>
</tr>
<tr>
<td>Risedronate Patients</td>
<td>12215 (0)</td>
<td>12202 (13)</td>
<td>6847 (19)</td>
<td>4319 (27)</td>
<td>2584 (29)</td>
</tr>
</tbody>
</table>
>7,000 Women: Age 73 years, T-score <-2.5 or <-1.5 and 2 Vertebral Fractures:

70% Reduction in vertebral fractures
41% Reduction in hip fractures
25% reduction in non-vertebral fractures

** NO REDUCTION IN MORTALITY **
Notes on bisphosphonate trials

- Fracture studies in postmenopausal women only

- Mean Age: 71, 69, 73 years

- All had osteoporosis: T-score $<-2.5$ or $<-1.0$ and prevalent spine fracture

- Oral trials used daily dose of 5/10mg or 2.5/5mg
Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

ZA 5mg I.V. annually Vs Placebo in 2,127 men & women ≥50 years following hip fracture

Significant reduction in:
FRACTURES &
** DEATH **
Oral bisphosphonates are associated with reduced mortality after hip fracture

L. A. Beaupre · D. W. Morrish · D. A. Hanley · W. P. Maksymowych · N. R. Bell · A. G. Juby · S. R. Majumdar

Received: 8 June 2010 / Accepted: 1 September 2010 / Published online: 4 November 2010
© International Osteoporosis Foundation and National Osteoporosis Foundation 2010

Abstract
Summary Intravenous bisphosphonates reduce mortality following hip fracture. We determined whether new use of oral bisphosphonates was also associated with reductions in mortality in 209 hip fracture patients. Oral bisphosphonate exposure led to relative reduction of 8% per month of use (p=0.001) or about a 60% reduction in mortality per year of use.

Oral bisphosphonate use was associated with 8% lower mortality per month of use
Assessment of Mortality in Patients Enrolled in a Risedronate Clinical Trial Program: A Retrospective Cohort Study

Michael Steinbuch,* Ralph B. D’Agostino,† Jack S. Mandel,** Edward Gabrielson,$ Michael R. McClung,$∥ Annette Stemhagen,¶ and Albert Hofman**

*Procter & Gamble Pharmaceuticals, Mason, Ohio; †Department of Mathematics, Statistics, and Public Health, Boston University, Boston, Massachusetts; ‡Exponent, Menlo Park, California; §Johns Hopkins University School of Medicine, Baltimore, Maryland; ¶Oregon Osteoporosis Center, Portland, Oregon; ||Covance Periapproval Services, Inc., Radnor, Pennsylvania; and **Erasmus University Medical School, Rotterdam, The Netherlands

Received October 19, 2001

INTRODUCTION

Risedronate, a pyridinyl bisphosphonate, has been shown in large clinical trials to be effective in the prevention and treatment of osteoporosis. Analysis

Bisphosphonates inhibit bone resorption and have been widely used for several years in the treatment of osteoporosis.
But drugs are bad!

First our parents told us....

Then our teachers....
Then The Dentist Told Us.....
Then the our surgeons told us...

**Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women**

**Conclusion** Among older women, treatment with a bisphosphonate for more than 5 years was associated with an increased risk of subtrochanteric or femoral shaft fractures; however, the absolute risk of these fractures is low.

*JAMA. 2011;305(8):783-789*
Even the cardiologists are telling us...
Even the cardiologists are telling us…

HR: 1.51, 95% CI: 0.97-2.40

Tonic-clonic seizure as the presentation symptom of severe hypocalcemia secondary to zoledronic acid administration.

Prolonged hypocalcemia after treatment with zoledronic acid in a patient with prostate cancer and vitamin D deficiency.

Hypocalcaemia after intravenous bisphosphonate: read the product information first.
Breay S. BMJ 2004; 328: 1439
So to minimize risk…

• Ensure patient is clinically “stable”
• Ensure adequate calcium and vitamin D
• (We bolus with vitamin D)
• Ensure renal, liver function normal
• Ensure calcium metabolism normal
Bisphosphononate Summary

• Most Widely prescribed class of medication
• Different mechanism of action, doses and dosing regimens – can be difficult to follow
• Rapid anti-fracture effect as early as 6 months
• Decrease bone turnover by 30 to 70%.
• Sustained fracture benefit and safety with 5-10 years of therapy
• Can cause myalgias, arthralgias and flu like symptoms and oral Rx prone to GI upset
• Risk of serious side-effects very low..
• Long-term risks under intense scrutiny
Effect of PTH 1-34 on Fracture Risk in Postmenopausal Women

- **Placebo**: RR = 0.35, 95% CI = 0.22-0.55.
- **20 µg PTH**: RR = 0.31, 95% CI = 0.19-0.50.
- **40 µg PTH**: RR = 0.47, 95% CI = 0.25-0.88.

† RR = 0.46, 95% CI = 0.25-0.88.

*RR* indicates relative risk, and *CI* indicates confidence interval.
Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

- 3 year trial of Dmab 60mg s/c every 6 months in 7,800 postmenopausal women (72 yr)

- Significant Reduction in:
  - Vertebral fractures
  - Non-vertebral fractures
  - Hip fractures

NON-SIGN RED. IN DEATH: 1.8% Vs 2.3%
# Comparative Effectiveness of Current Treatments

*Adapted with Modifications from MacLean C. Ann Intern Med 2008; 148:197-213.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral</th>
<th>Hip</th>
<th>Non-vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Etidronate</td>
<td>Good</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Good</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Risedronate</strong></td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Good</td>
<td>-</td>
<td>Fair</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Good</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Fair</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Strontium Ranelate*</td>
<td>Good</td>
<td>BIAS</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Denosumab</strong></td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>
# Dosing of approved Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Alendronate</td>
<td>10mg, 70mg</td>
<td>Oral</td>
<td>Daily, weekly</td>
</tr>
<tr>
<td>Etidronate</td>
<td>400mg</td>
<td>Oral</td>
<td>quarterly</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>3mg, 150mg</td>
<td>IV, Oral</td>
<td>3 &amp; 1 month</td>
</tr>
<tr>
<td>Risedronate</td>
<td>5, 35mg</td>
<td>Oral</td>
<td>Daily, weekly</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>5mg</td>
<td>IV</td>
<td>Annual</td>
</tr>
<tr>
<td>Estrogen</td>
<td>varies</td>
<td>Topical, oral</td>
<td>Varies</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>20mcg</td>
<td>Sub cut</td>
<td>Daily</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>60mg</td>
<td>oral</td>
<td>Ddaily</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>200mcg</td>
<td>nasal</td>
<td>Daily</td>
</tr>
<tr>
<td>Strontium Ranelate*</td>
<td>2grams</td>
<td>Oral</td>
<td>Daily</td>
</tr>
<tr>
<td>Denosumab</td>
<td>60mg</td>
<td>Sub cut</td>
<td>6 monthly</td>
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</table>
Combination therapy

- Many Studies, no fracture data
Why do we need New Treatments?

• Treatment reduces fracture risk, it does not eliminate it

• Side effects & Long-term safety concerns

• Special populations: children, ESRD, hyperparathyroidism

• The holy grail: a cure?
LOFT Study
ASBMR 2014, USA

- 16,713 women, 40 countries
- Elderly women (mean age 73) with osteoporosis
- 57% caucasian, 17.5% asian, 23% multi-racial
- All calcium & vitamin D if appropriate
- Odonacatib 50mg (N=8357) PO weekly or Placebo (N=8356)
- Significant reduction in Fracture (P<0.01):
  - Clinical Vertebral RR: 72%, Hip: 47%, NV: 23%

** Similar Aes; No reduction in mortality
Sclerostin Inhibition for Osteoporosis — A New Approach
Carolyn B. Becker, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Romosozumab in Postmenopausal Women with Low Bone Mineral Density

Similar results with Blosozumab...
Fall Prevention

• Traditionally Osteoporosis therapies have focussed on weak bones

• >90% of non-vertebral fractures occur following a fall

• Fall prevention is complex and poor resourced here for most at highest risk
Anabolic Muscle therapies are on the way....
Muscle Therapies

- Anabolic Steroids
- S.A.R.M.s
- Myostatin Analogues
One Day...
Epidemiology: Incidence & Mortality


- Ireland: incidence rising in Ireland… while downward trend in other OECDs

- Despite progress in care and Rx, 1-year mortality hasn’t changed much (UK**):
  - 1997: 20%
  - 2011: 17%
  - GUH: 26% overall, 33% for men
WHY?
The ‘typical’ care pathway:


- 2009: Admitted with hip fracture: Rx with calcium and vitamin D. Drug Rx recommended… didn’t happen

- 2012: 2 vertebral fractures: No Rx

- Admitted 2014 with Humeral fracture: Surgery only…fell on the ward prior to d/c - hip fracture. Rx, but..
‘The persistent chasm between best evidence and best practices in osteoporosis is an international phenomenon.

There is considerable evidence that individuals in many developed nations who experience a fragility fracture are not receiving adequate osteoporosis management....

....many go on to experience subsequent fractures, and many have never been told they may have osteoporosis, let alone been tested or treated.

Curtis JR, JBMR Jan 2009
Fig. 1. Estimated sales (DDD/100 population aged 50+ years) from 2001 to 2011 in the European Union. Reproduced from Hernlund and colleagues,\(^1\) Arch Osteoporos. 2013;8:136, with kind permission from Springer Science and Business Media. DDD = defined daily dose.
GUH hip fractures

- Median Age: 83 years
- 74% female
- Mean Length of Stay 19 days
- 1-year Mortality 26% (men >30%)
- <10% Rx for their osteoporosis
## Scorecard for Osteoporosis in Europe

### Burden of disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Units</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Hip fracture risk</td>
<td>Age-standardised incidence of hip fracture in women</td>
<td>rate/100,000</td>
<td></td>
</tr>
<tr>
<td>Fracture risk</td>
<td>All osteoporotic fractures in men and women</td>
<td>rate/1000 &gt;50 years</td>
<td></td>
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<tr>
<td>Lifetime risk</td>
<td>Lifetime risk of hip fracture (women aged 50y)</td>
<td>%</td>
<td></td>
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<tr>
<td>FRAX risk</td>
<td>Men and women with a &gt; 10% ten year probability of a major fracture</td>
<td>% in 50-89 years age range</td>
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<tr>
<td>Fracture projections</td>
<td>Increase in fracture number 2010-2025</td>
<td>% &gt;50 years</td>
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### Policy framework

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<th>Category</th>
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<tbody>
<tr>
<td>Quality of data</td>
<td>Data on hip fracture rates</td>
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<tr>
<td>National health priority</td>
<td>The presence of government backed NHP</td>
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<tr>
<td>Care pathway</td>
<td>Management in primary care</td>
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<tr>
<td>Specialist training</td>
<td>Osteoporosis an established specialty</td>
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<tr>
<td>Society support</td>
<td>Patient support societies</td>
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### Service provision

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<td>Treatment</td>
<td>Reimbursement and problems that arise</td>
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<tr>
<td>Availability of DXA</td>
<td>DXA units available</td>
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<tr>
<td>Access to DXA</td>
<td>Reimbursement and problems that arise</td>
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<tr>
<td>Risk models</td>
<td>Availability of country-specific risk models and guidance</td>
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<tr>
<td>Guideline quality</td>
<td>Quality and scope of guidelines for assessment and treatment</td>
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<tr>
<td>Liaison service</td>
<td>Provision for fracture liaison services</td>
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<tr>
<td>Quality indicators</td>
<td>Presence and use of quality indicators</td>
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### Service uptake

<table>
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<tr>
<td>Risk models</td>
<td>FRAX calculations</td>
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</tr>
<tr>
<td>Treatment gap</td>
<td>Proportion of women at high risk who are untreated</td>
<td></td>
</tr>
<tr>
<td>Waiting time</td>
<td>Average waiting time for hip surgery</td>
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</table>
Scorecard Domains

- Burden of disease
- Policy Framework
- Service Provision
- Service uptake
“The aim is to push beyond standard-setting… and to make those standards a living reality for people everywhere”.

Mary Robinson, former President
GUH HOOF Project

• Typical hip Fracture patient:
  – 16% taking calcium and vitamin D
  – <10% on pharmacologic OP therapy
  – Same among patents with prior fracture!

• Following Programme Establishment:
  – Approx 90% on calcium & vitamin D
  – 80% of Osteoporosis medication
IOF Capture The Fracture Programme:
Map of Best Practice
http://www.capturethefracture.org/map-of-best-practice
Capture the Fracture: 13Domains

• Identification

• Evaluation and Rx: Tests, Rx, Falls etc

• Communication Strategy

• Long-term management

• Database
Submit Your Application

GET MAPPED
Submit your FLS and gain visibility on our Map of Best Practice at: www.capturethefracture.org
RESOURCES
I.S.C.D. Annual Meeting
2016 Galway, Ireland

“Quality Matters”

Céad Míle Fáilte!
Thank you

Questions?