WHAT IS OSTEOPOROSIS?

Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone tissue, leading to an increased risk of fracture. Osteoporosis causes a net loss of bone strength, as a result even a slight bump or fall can lead to a broken bone (referred to as a fragility fracture). Osteoporosis has no signs or symptoms until a fracture occurs – this is why it is often called a ‘silent disease’.

Osteoporosis affects all bones in the body; however, fractures occur most frequently in the vertebrae (spine), wrist and hip. Osteoporotic fractures of the pelvis, upper arm and lower leg are also common. Osteoporosis itself is not painful but the broken bones can result in severe pain, significant disability and even mortality. Both hip and spine fractures are associated with a higher risk of death - 20% of those who suffer a hip fracture die within 6 months after the fracture.

A Common Disease

It is estimated that worldwide an osteoporotic fracture occurs every three seconds. From 50 years of age, one in three women and one in five men will suffer a fracture in their remaining lifetime. For women, the risk of hip fracture is higher than the risk of breast, ovarian and uterine cancer combined. For men, the risk is higher than the risk for prostate cancer. Approximately 50% of people with one osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture.

A Growing Public Health Problem

The risk of sustaining a fracture increases exponentially with age due not only to the decrease in bone mass, but also due to the increased rate of falls among the elderly. The elderly represent the fastest growing segment of the population and as life expectancy increases for the majority of the world’s population, the financial and human costs associated with osteoporotic fractures will increase dramatically unless preventive action is taken.

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All references included in this report are available at the following link:
www.worldosteoporosisd/2016-report/references
Bone health in 2016: Gaps and solutions

This Report provides a comprehensive, global overview of the state of osteoporosis care for individuals at high-risk of suffering fragility fractures. Ten ‘gaps’ have been identified which can be clustered into four major themes:

1. CASE FINDING AND MANAGEMENT:
   - Gap 1: Secondary fracture prevention
   - Gap 2: Osteoporosis induced by medicines
   - Gap 3: Diseases associated with osteoporosis
   - Gap 4: Primary fracture prevention for individuals at high risk of fracture

2. PUBLIC AWARENESS:
   - Gap 5: The importance of staying on treatment
   - Gap 6: Public awareness of osteoporosis and fracture risk
   - Gap 7: Public awareness of benefits versus risks of osteoporosis treatment

3. GOVERNMENT AND HEALTH SYSTEM ISSUES:
   - Gap 8: Access and reimbursement for osteoporosis assessment and treatment
   - Gap 9: Prioritization of fragility fracture prevention in national policy

4. LACK OF DATA:
   - Gap 10: The burden of osteoporosis in the developing world

During 2016, the first of the Baby Boomers will celebrate their 70th birthdays. As a direct consequence, the increasing burden of fragility fractures will place severe strains on the capacity and finances of healthcare systems. Thankfully, this is a catastrophe that would be entirely preventable if the solutions to each gap identified in this report were to be implemented worldwide.

With regard to case finding and management, widespread implementation of Fracture Liaison Services and Orthogeriatrics Services would ensure that healthcare systems can always respond to the first fragility fracture, in order to prevent the second. Healthcare professionals and patients are aware of which medicines the patient has been prescribed. Accordingly, when drugs that have an adverse effect on bone health are necessarily used to manage other conditions, adherence to the numerous clinical guidelines available to prevent bone loss and fractures should be the norm. Among individuals who suffer diseases in which osteoporosis is a common comorbidity, osteoporosis and fracture risk assessment should be a standard component of managing the disease in question. Finally, fracture risk assessment tools, such as FRAX®, are now readily available to pre-emptively identify those individuals who are at high-risk of suffering their first fragility fracture.

Public awareness of osteoporosis, and the fragility fractures it causes, is low in many countries. A determined global effort is required, involving healthcare professionals and their organisations, patient societies and policymakers, to provide the public with clear, consistent and compelling messages regarding bone health. The most obvious initial target group for such messages comprises those individuals who have been initiated on osteoporosis treatment, to ensure that they stay on that treatment. For many people, the association between osteoporosis and fracture risk is not clear. A pressing need also exists for evidence-based communications which highlight the risk that untreated osteoporosis poses to sufferers’ quality and quantity of life.

In contrast with other comparable common non-communicable chronic diseases, osteoporosis has often not attracted a commensurate level of attention from health providers and governments. Given the current and imminent future burden imposed by this disease, that is a position which policymakers can no longer afford to take. Access to treatment cannot be impeded by inadequate access to bone mineral density testing, or inadequate reimbursement policies for treatments. Further, osteoporosis and fragility fracture prevention should feature as a National Health Priority in all countries. Action is needed now, and not in 10 or 20 years’ time when it will already be too late.

Finally, given current projections indicating that the burden of fragility fracture will shift to the developing world over the next four decades, it is imperative that governments, key opinion leaders and national patient societies work together now to ensure that epidemiological data are available to inform policy development in these countries.

There is much to be done. However, all ten of these gaps have been closed somewhere in the world. The task now facing all of us is to ensure the dissemination and adoption of these best practice examples, adapted for local considerations, in order to tackle the current, and future, burden of fragility fractures worldwide.
GAP 1: SECONDARY FRACTURE PREVENTION
Fragility fractures are common and expensive

The clinically important consequence of osteoporosis is a fragility fracture. Fragility fractures, also referred to as low or minimal trauma fractures, usually happen as a result of a fall from standing height, and occur most commonly at the spine, wrist, hip, humerus (upper arm) or pelvis. Among people over 50 years of age, half of women and a fifth of men will suffer a fragility fracture during their remaining lifetime. Arguably, hip fractures impose the greatest burden on sufferers and their families:

- Fewer than half of people who survive a hip fracture will walk unaided again and in many cases they will never regain their former degree of mobility.
- A year after hip fracture, 60% of sufferers require assistance with activities such as feeding, dressing or toileting, and 80% need help with activities such as shopping or driving.
- Between 10-20% of sufferers will become residents of care homes in the year following a hip fracture.
- Mortality 5 years after hip or vertebral fracture is about 20% in excess of that expected; Most excess deaths occur in the first 6 months after hip fracture.

As shown in figure 1, recent estimates of the annual incidence of hip fracture in the European Union and some of the most populous countries elsewhere highlight the scale of the current burden, a burden which is set to grow rapidly as the world’s population ages.

The economic burden imposed by fragility fractures is staggering:

**EUROPEAN UNION:** In 2010, the 27 countries of the EU – the current EU28 countries prior to Croatia’s entry - were estimated to have spent €37 billion on fragility fractures, a cost which is expected to increase by 25% by 2025.

**USA:** The cost of fragility fractures in the United States in 2015 was estimated to be in excess of US$20 billion. Analysis suggests that Medicare bears 70% of the costs of fracture and osteoporosis-related care.

**CHINA:** In 2010, the cost imposed by fractures among people with osteoporosis was estimated to be in excess of US$9 billion, which is expected to rise to US$25 billion by 2050.

However, fragility fractures need not be an inevitable consequence of ageing.

**Secondary fractures can be prevented**

Since the 1990s, a broad range of effective treatments for osteoporosis have become available throughout the world. Osteoporosis treatments can be taken as daily, weekly or monthly tablets, or as daily, quarterly, six-monthly or annual injections. Several Cochrane Collaboration systematic reviews of secondary fracture prevention (i.e. reduction in rates of re-fracture) have been published for alendronate, etidronate and risedronate. The findings of the Cochrane reviews are summarized below, including reference to relative risk reduction (RRR: a halving of fracture risk on treatment represents an RRR of 50%) and absolute risk reduction (ARR: the absolute percentage difference in fracture rates between those treated and those receiving placebo, which depends upon the background fracture risk of the population studied):

- **Alendronate:** Clinically important and statistically significant reductions in vertebral (RRR 45%, ARR 6%), non-vertebral (RRR 23%, ARR 2%), hip (RRR 53%, ARR 1%) and wrist fractures (RRR 50%, ARR 2%) were observed, designated as ‘gold’ level evidence.
- **Etidronate:** A statistically significant reduction was observed only for vertebral fractures (RRR 47%, ARR 5%). The level of evidence for all outcomes was designated ‘silver’.
- **Risedronate:** Statistically significant reductions in vertebral (RRR 39%, ARR 5%), non-vertebral (RRR 20%, ARR 2%) and hip (RRR 26%, ARR 1%) fractures were observed. The level of evidence was designated ‘gold’ for vertebral and non-vertebral fractures, and ‘silver’ for hip and wrist fractures.

A Cochrane systematic review of intravenous zoledronate - administered as an annual infusion - for postmenopausal osteoporosis, is planned but was not available at the time this report was written. The HORIZON Pivotal Fracture Trial (PFT) evaluated zoledronate for the treatment of postmenopausal osteoporosis. Whilst the majority (>60%) of study participants had at least one prevalent vertebral fracture at recruitment, this was not specifically a secondary fracture prevention trial. However, the HORIZON Recurrent Fracture Trial (RFT) evaluated...
zoledronate for treatment of individuals who had undergone repair of a hip fracture and were unable or unwilling to take an oral bisphosphonate. Statistically significant reductions in any new clinical fracture (RRR 35%, ARR 5.3%), clinical non-vertebral fracture (RRR 27%, ARR 3.1%) and new clinical vertebral fracture (RRR 46%, ARR 2.1%) were observed. A non-significant trend towards reduction in hip fracture (RRR 30%, ARR 1.5%) was observed. The safety analysis revealed a statistically significant reduction in deaths from any cause for the individuals treated with zoledronate (RRR 28%, ARR 3.7%).

A Cochrane systematic review for denosumab – administered as a six-monthly sub-cutaneous injection - for postmenopausal osteoporosis, is also awaited. The FREEDOM study evaluated denosumab for the treatment of postmenopausal osteoporosis. Whilst almost half (45%) of study participants had at least one prevalent vertebral fracture on recruitment, this was not specifically a secondary fracture prevention trial. A post-hoc analysis of this study ascertained the impact of denosumab on the occurrence of secondary fragility fractures. A statistically significant reduction in any secondary fragility fracture (RRR 39%, ARR 6.8%) was observed. Significant reductions were also observed for the sub-groups of participants who had vertebral fractures (RRR 35%, ARR 6.6%) and non-vertebral fractures (RRR 34%, ARR 6.1%) at baseline.

Raloxifene is currently the only selective estrogen receptor modulator (SERM) used in clinical practice for fracture prevention. Among the sub-group of women in the MORE study who had a prevalent vertebral fracture at baseline, those receiving the licensed 60 mg dose of raloxifene suffered significantly fewer new vertebral fractures compared to placebo (RRR 30%, ARR 6%). No significant difference was observed for rates of non-vertebral fractures for women treated with raloxifene as compared to placebo. With regard to hormone replacement therapy (HRT), there is no specific evidence in the secondary fracture prevention setting.

The parathyroid hormone (PTH) analogue teriparatide - administered by subcutaneous injection once daily - is an anabolic agent which directly stimulates osteoblastic bone formation. Teriparatide was evaluated for the treatment of postmenopausal osteoporosis among women with at least one vertebral fracture at baseline. Participants who received the licensed dose of 20 µg per day suffered significantly fewer new vertebral fractures (RRR 65%, ARR 9.3%) and non-vertebral fragility fractures (RRR 53%, ARR 2.9%).

Finally, a pre-planned sub-analysis of postmenopausal women with osteopenia and a prevalent vertebral fracture, who were recruited to the SOTI and TROPOS studies of strontium ranelate, reported a significant reduction in the incidence of new vertebral fractures (RRR 37%, ARR 8.1%). The SOTI study evaluated strontium ranelate specifically in a secondary prevention population, because all participants had radiographic evidence of at least one vertebral fracture. However, no statistically significant effect of treatment was observed on the incidence of non-vertebral fractures. Approximately 55% of women recruited to the TROPOS study had a history of any vertebral or non-vertebral fracture. However, the impact of treatment on this prevalent fracture subgroup of the study population was not reported.

Thus, a diverse array of effective osteoporosis treatments is available to reduce the risk of second and subsequent fractures among individuals presenting with their first fragility fracture.

The care gap

In 2012, an IOF report issued for World Osteoporosis Day was devoted to the global Capture the Fracture® Campaign33, 34. Approximately half of hip fracture patients suffer a prior fragility fracture in the months or years before breaking their hip, representing an obvious opportunity and, indeed, imperative for assessment and intervention to prevent future fractures. The report also cited numerous audits undertaken across the world to establish what proportion of fracture patients received the osteoporosis care that they needed: in the absence of a systematic approach, less than a fifth received such care. Whilst some exciting progress has been made to close this care gap many publications and initiatives since 2012 bear testament to the fact that there is still a huge amount of work to be done throughout the world:

**ASIA:** China41, Japan42-44, South Korea45-47, Thailand48

**EUROPE:** Austria49, 50, France51, 52, Germany53, 54-56, Ireland57, 58, Norway60, 61, Spain54, Sweden62, UK63-69

**MIDDLE EAST:** Saudi Arabia70

**NORTH AMERICA:** Canada71-74, USA75, 76, 77-87

**OCEANIA:** Australia88-91, New Zealand81-93

Since the turn of the century, clinically effective models of care have been developed in many countries to close the secondary prevention care gap in a highly cost-effective manner.

‘Approximately 50% of people with one osteoporotic fracture will have another, with the risk of new fractures rising exponentially with each fracture. The majority of fragility fracture patients never learn what caused their fracture to happen, or receive treatment to prevent it from happening again. Evidently, this is a missed opportunity to identify and treat those at greatest risk of disabling and costly secondary fractures.’35

**Professor Cyrus Cooper**
HIP FRACTURE PATIENTS

NON-HIP FRAGILITY FRACTURE PATIENTS

INDIVIDUALS AT HIGH RISK OF 1ST FRAGILITY FRACTURE OR OTHER INJURIOUS FALLS

OLDER PEOPLE

Figure 2. Orthogeriatrics Services and Fracture Liaison Services as components of a systematic approach\(^9^7\)

Models of care: Orthogeriatrics Services and Fracture Liaison Services

In response to the well documented secondary fracture prevention care gap, innovators throughout the world have developed models of care designed to ensure that health systems respond to the first fracture to prevent second and subsequent fractures:

- **Orthogeriatrics Services (OGS):** The need for effective orthopaedic – geriatric co-care of patients admitted to hospital with hip fractures is well recognised in professional guidance\(^9^5-, 9^6\). Such models of care focus on expediting surgery, ensuring optimal management of the acute phase through adherence to a care plan overseen by senior orthopaedic and geriatrician/internal medicine personnel, and delivery of secondary fracture prevention through osteoporosis management and falls prevention.

- **Fracture Liaison Services (FLS):** The Fracture Liaison Service (FLS) model of care has also been adopted in many countries. The purpose of an FLS is to ensure that all patients aged 50 years or over, who present to urgent care services with a fragility fracture, undergo fracture risk assessment and receive treatment in accordance with prevailing national clinical guidelines for osteoporosis. The FLS also ensures that falls risk is addressed among older patients through referral to appropriate local falls prevention services.

These two service models are entirely complementary. As adoption of OGS for hip fracture sufferers becomes more widespread, OGS are increasingly likely to deliver secondary preventive care for these patients. As hip fractures constitute approximately 20% of all clinically apparent fragility fractures, in health systems which have implemented an OGS, FLS will provide secondary preventive care for the other 80% of fragility fracture sufferers who have experienced fractures of the wrist, humerus, spine, pelvis and other sites. This “division of labour” is illustrated in the falls and fractures pyramid in figure 2, which was first presented in policy developed by the Department of Health for England in 2009\(^9^7\). A similar approach has been advocated in Australia\(^9^5\), Canada\(^1^\), New Zealand\(^9^3\) and the United States 99, 100.

Secondary fracture prevention — and OGS and FLS as a reliable means to deliver this care to fracture patients — has featured in a growing number of clinical guidelines and government policies.

Guidelines, policy and national secondary fracture prevention initiatives

During the last 15 years, the number of clinical guidelines from societies and policies from governments which highlight the importance of secondary fracture prevention has increased considerably. Furthermore, a number of national campaigns to drive widespread adoption of OGS and/or FLS have been undertaken. Examples from several countries include:

**AUSTRALIA AND NEW ZEALAND:** Clinical guidelines from the Australian Commission on Quality and Safety in Healthcare\(^1^0^1-, 1^0^3\), Australian and New Zealand (ANZ) Hip Fracture Registry\(^9^5\) and Royal Australian College of General Practitioners\(^1^0^4\). Policy initiatives in Australia from state governments in New South Wales\(^9^8-, 1^0^5\), South Australia\(^1^0^6\) and Western Australia\(^1^0^7-, 1^0^9\). A position paper and call to action from the ANZ Bone and Mineral Society\(^9^1\). An Australian national alliance focused on secondary fracture prevention is in development in 2016\(^1^1^0\). A FLS implementation initiative developed by the ANZ Bone and Mineral Society\(^1^1^1\). A multi-
WHAT IS OSTEOSOROSIS?

OSTEOSOROSIS IS A DISEASE CHARACTERIZED BY LOW BONE MASS AND DETERIORATION IN THE MICROARCHITECTURE OF BONE TISSUE, LEADING TO AN INCREASED RISK OF FRACTURE. OSTEOSOROSIS CAUSES A NET LOSS OF BONE MASS.

Sector initiative in New Zealand focused on implementation of OGS and FLS112, 113. An ANZ Clinical Care Standard for hip fracture114.

CANADA: Clinical guidelines from Osteoporosis Canada115. A FLS implementation initiative led by Osteoporosis Canada79, including Quality Standards for FLS endorsed by many learned societies14.

JAPAN: The Japanese Osteoporosis Society developed an accreditation programme for physicians and coordinators working in Osteoporosis Liaison Services (which deliver FLS and a systematic approach to primary fracture prevention)116.

SINGAPORE: The Osteoporosis Patient Targeted and Integrated Management for Active Living (OPTIMAL) Programme was funded by the Singapore Ministry of Health to deliver secondary fracture prevention in the 5 public hospitals in existence in Singapore in 2008117. The programme was subsequently expanded to include the 18 polyclinics in Singapore.

UNITED KINGDOM: Clinical guidelines from the National Institute for Health and Care Excellence (NICE)118-123 and the National Osteoporosis Guideline Group (NOGG)124. Establishment and government funding of the National Hip Fracture Database (NHFD)125. Policy from the Department of Health97, 126 and financial incentives for primary127 and secondary care128. British Orthopaedic Association Standards for Trauma (BOASTs) on hip fracture care129 and FLS130. Clinical Standards for FLS from the National Osteoporosis Society (NOS)131, in addition to a NOS FLS Toolkit132 and NOS FLS Service Development Team.

UNITED STATES OF AMERICA: Clinical guidelines from the Endocrine Society133 and National Osteoporosis Foundation (NOF)134. Following the Surgeon General’s Report on Bone Health in 20041 and subsequent publication of the National Action Plan on Bone Health in 2008135, the National Bone Health Alliance (NBHA) was formed in late 2010136. NBHA has developed an award winning disease awareness campaign relating to secondary fracture prevention, 2Million2Many137, and an FLS implementation initiative, Fracture Prevention CENTRAL137. Quality measures have been developed by The Joint Commission and endorsed by the National Quality Forum138. NBHA and NOF have developed a Qualified Clinical Data Registry (QCDR) which is approved by the Centers for Medicare and Medicaid Services (CMS)139. The QCDR is focused on measuring, reporting and improving patient outcomes in osteoporosis and post-fracture care. NOF has developed a FLS accreditation programme139.

The IOF Capture the Fracture® Programme

The IOF Capture the Fracture® Programme aims to support implementation of FLS throughout the world. During the last 4 years, the programme has gained considerable momentum. The key elements of Capture the Fracture® are:

- Website: The Capture the Fracture® website - www.capture-the-fracture.org - provides a comprehensive suite of resources to support healthcare professionals and administrators to establish a new FLS or improve an existing FLS.

- Webinars: An ongoing series of webinars provide an opportunity to learn from experts across the globe who have established high-performing FLS and contributed to development of guidelines and policy on secondary fracture prevention.

- Best Practice Framework: The Best Practice Framework (BPF), currently available in 8 major languages, sets an international benchmark for FLS by defining essential and aspirational elements of service delivery. The BPF serves as the measurement tool for IOF to award “Capture the Fracture® Best Practice Recognition” in celebration of successful FLS worldwide. The 13 globally-endorsed standards of the BPF have been published in Osteoporosis International140. The BPF tool has been tested in a range of health settings across the globe. Initial findings during the first 12 months confirmed a significant heterogeneity in service provision and highlighted the importance of a global approach to ensure high quality secondary fracture prevention services141.

The BPF Map of Best Practice shown in figure 3 has recognised FLS from across the world142. IOF encourages leaders of FLS to share their experience through a submission for Best Practice Recognition at http://www.capture-the-fracture.org/best-practice-framework.
GAP 2:
OSTEOPOROSIS INDUCED BY MEDICINES
Many widely used medicines have been associated with decreases in bone mineral density and/or increased fracture incidence, although these links have not been proven as causal in every case. Such evidence has been reported for the following classes of agents:

- Glucocorticoids
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors
- Thiazolidinediones
- Anticonvulsants
- Medroxyprogesterone acetate
- Hormone deprivation therapy
- Calcineurin inhibitors
- Chemotherapies
- Anticoagulants

A 2014 review described the potential pathogenesis of bone loss associated with all of these classes of medicines. This report will focus on three very commonly used agents: glucocorticoids for a range of conditions, androgen deprivation therapy for treatment of prostate cancer in men, and aromatase inhibitors for treatment of hormone receptor-positive breast cancer in women.

Glucocorticoid-induced osteoporosis

Pathogenesis of glucocorticoid-induced osteoporosis
Glucocorticoids (GCs) affect function and numbers of the three major types of bone cells:

- **Osteoclasts**: Stimulation by GCs results in prolonged survival of osteoclasts leading to excessive bone resorption, particularly in trabecular bone in the spine.

- **Osteoblasts**: By reducing the recruitment of the precursors to osteoblasts the number of mature osteoblasts is reduced, resulting in decreased bone formation.

- **Osteocytes**: Osteocyte apoptosis (cell death) is triggered by GCs and may contribute to an increase in fracture risk prior to a reduction in bone mineral density (BMD).

In 2014, Henneicke and colleagues published a detailed review of the direct and indirect effects of GCs on bone.

Glucocorticoid use and fracture incidence
GCs are very commonly used to control inflammation in the setting of a broad range of conditions including autoimmune, dermatological and respiratory diseases, and malignancies and organ transplants. Estimates suggest that 1 in 13 adults aged 18 years and over have been prescribed an oral GC at some stage of their life.

Up to 30-50% of patients receiving chronic glucocorticoid therapy experience clinically apparent fragility fractures and/or asymptomatic vertebral fractures, making GC-induced osteoporosis the leading cause of secondary osteoporosis. Meta-analysis has shown previous GC use to be associated with a relative risk of 2 for any fracture at the age of 50 years and 1.7 at the age of 85 years. For osteoporotic fracture the range of relative risk is 2.6 and 1.7; and for hip fracture 4.4 and 2.5 for the same age groups.

**Prevention and treatment of glucocorticoid-induced osteoporosis**

Clinical guidelines for the prevention and treatment of GC-induced osteoporosis are available in many countries, including Austria, Australia, Belgium, Brazil, France, Japan, The Netherlands, Spain, UK and the United States. Furthermore, the European League Against Rheumatism (EULAR) and a Joint Guideline Working Group of IOF and the European Calcified Tissue Society (ECTS) have produced internationally relevant guidance. Whilst the detail of individual guidelines varies somewhat, the common theme is that individuals receiving chronic GC therapy are at increased risk of fracture on account of taking GCs, and, in a significant proportion, the risk is great enough to warrant the offer of preventive treatment.

**The care gap**
In 2014, a systematic literature review of osteoporosis management among GC users evaluated studies conducted between 1999 and 2013. Among the various studies reviewed, the proportion of patients reported to have received BMD testing ranged from 0% to 60%, and osteoporosis treatment ranged from 0% to 78%. The majority of studies (>80%) identified that less than 40% of chronic oral GC users underwent BMD testing or osteoporosis treatment. Accordingly, despite widely available guidelines a significant care gap exists worldwide in prevention and treatment of GC-induced osteoporosis.
Quality improvement initiatives

It is clear that major efforts are now required to close the GC-induced osteoporosis care gap. Healthcare professionals, health administrators and policymakers should seek to audit what proportion of long term GC users in their health systems are currently receiving guideline-based care. The following quality improvement initiatives from Australia and the United States could inform efforts to routinely deliver best practice elsewhere:

AUSTRALIA: A multifaceted education programme delivered in Tasmania, which incorporated academic detailing of general practitioners and community pharmacists, increased the use of osteoporosis prevention strategies in long term oral GC users162. The use of osteoporosis treatments was 31% prior to the intervention, increasing to 57% after the intervention (highly significant, p<0.0001).

UNITED STATES OF AMERICA: The Geisinger Health System in the United States implemented an organized programme of care - GIOP (Glucocorticoid-Induced Osteoporosis Program) – in order to improve preventive care for members163. The programme goals were to identify patients at risk of fracture, provide education, redesign and implement new pathways of care, and monitor outcomes. Key outcomes at 12 months included:

- Patient retention of knowledge, frequent exercise, and 25(OH)-vitamin D concentrations all significantly improved.
- A significant decrease in GC dose was observed.
- 91% of patients considered at high fracture risk were taking a bisphosphonate or teriparatide at 1 year, and 96% of patients overall were adherent to their prescribed regimen of calcium, vitamin D, and prescription treatment, where indicated.

Androgen Deprivation Therapy-induced osteoporosis

Pathogenesis of Androgen Deprivation Therapy-induced osteoporosis

Androgen Deprivation Therapy (ADT), in the form of gonadotropin-releasing hormone agonists (GnRHa), limits the production of testosterone and estradiol, leading to chemical castration143. GnRHa elicit this effect by reducing secretion of luteinizing hormone and follicle-stimulating hormone. This is a consequence of GnRHa binding to GnRH receptors in the pituitary gland and downregulating the gonadotropin-producing cells.

Androgen Deprivation Therapy use and fracture incidence

Prostate cancer is the most common non-cutaneous malignancy in men, with 1 in 6 men being diagnosed during their lifetime164. Approximately half of men diagnosed with prostate cancer will receive ADT at some stage after diagnosis165. In 2014, a meta-analysis of relevant studies reported that between 9% and 53% of survivors had osteoporosis166. A rapid decline in BMD is observed during the first year of ADT treatment167. A cohort study based on medical claims data from Medicare beneficiaries in the United States compared fracture rates for men with non-metastatic prostate cancer who initiated GnRH agonist treatment against a comparison group who did not receive GnRH agonist treatment168. The men treated with GnRHs had statistically significantly higher rates of any clinical fracture (relative risk [RR]: 1.2), vertebral fractures (RR: 1.5) and hip/femur fractures (RR: 1.3). Longer duration of treatment also conferred greater fracture risk.

Prevention and treatment of Androgen Deprivation Therapy-induced osteoporosis

Clinical guidelines relating to the prevention and treatment of ADT-induced osteoporosis are available in many countries, including Australia169, Belgium170, Canada171, New Zealand169, UK172 and the United States173, 174. Furthermore, the European Society for Medical Oncology has produced internationally relevant guidance175.

The care gap

The care gap for ADT-induced osteoporosis has not been documented as comprehensively as the secondary fracture prevention and GC-induced osteoporosis care gaps discussed above. However, local studies have been conducted in several countries, including Canada185, 176-178 India179 and the United States180-183. The rates of BMD testing and/or osteoporosis treatment varied from 9% to 59%, with on average less than a quarter of ADT treated men receiving appropriate care.

Quality improvement initiatives

Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in urology departments to establish what proportion of ADT treated patients have undergone osteoporosis assessment and received guideline-based care. A quality improvement initiative from the United States could inform efforts to routinely deliver best practice elsewhere184. In 2002, Kaiser Permanente Southern California (Kaiser SoCal) implemented the Healthy Bones Model of Care (HBM). This programme identifies individuals at high fracture risk and delivers guideline-based care in a systematic fashion. All Kaiser SoCal patients with prostate cancer newly diagnosed between 2003 and 2007
were identified through a cancer registry. Two study cohorts were subsequently created: any patient who had a bone density test at most 3 months before the first administration of ADT was assigned to the HBP group, and a contemporaneous control group was comprised of all others (the non-HBP group). The incidence of hip fracture was 70% lower in the HBP group compared to the non-HBP group.

**Aromatase Inhibitor-induced osteoporosis**

**Pathogenesis of Aromatase Inhibitor-induced osteoporosis**

Aromatase inhibitors (AIs) reduce estrogen levels by inhibition of the peripheral conversion of androgens to estrogens. This results in lower estrogen levels with a consequent increase in bone turnover and bone loss.

**Aromatase Inhibitor use and fracture incidence**

Breast cancer is the most common neoplasm and primary cause of cancer-related mortality in women, affecting 1 in 8 women worldwide.185 AIs currently represent the gold standard adjuvant treatment for postmenopausal women with hormone receptor-positive breast cancer.186 The annual rate of bone loss observed for women taking AIs of around 2.5% is elevated compared to healthy postmenopausal women who lose about 1% to 2% per year.187 Analysis of the Women’s Health Initiative Observational Study compared fracture rates among breast cancer survivors with women with no history of breast cancer at baseline.188 After adjustment for factors related to hormone levels, risk of falls, prior fracture history, medication use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was 15%. Studies comparing two commonly used AIs, anastrozole189 and letrozole190, with tamoxifen have reported significant increases in fracture risk for the AI treated patients. A comparative study of anastrozole with exemestane showed similar fracture rates.191 A position paper from the European Society for Clinical and Economical Aspects of Osteoporosis (ESCEO) has comprehensively documented studies on the skeletal effects of aromatase inhibitors.187

**Prevention and treatment of Aromatase Inhibitor-induced osteoporosis**

Clinical guidelines relating to the prevention and treatment of AI-induced osteoporosis are available in many countries, including Belgium, China, Germany, Italy, Lithuania, UK, and the United States. Furthermore, ESCEO has produced internationally relevant guidance.

**The care gap**

The care gap for AI-induced osteoporosis has not been documented as comprehensively as the secondary fracture prevention and GC-induced osteoporosis care gaps discussed above. However, local studies have been conducted in several countries, including the UK and the United States. The largest of these studies reported that less than half (44%) of women underwent BMD testing within 14 months of continuous AI use for at least 9 months. Furthermore, 75% and 66% of women failed to have BMD tests done during the second and third annual time periods after continuous AI use for almost 2 and 3 years, respectively.

**Quality improvement initiatives**

Local clinical leaders in osteoporosis care should explore opportunities for collaboration with colleagues in oncology departments to establish what proportion of AI treated patients have undergone osteoporosis assessment and received guideline-based care. The following quality improvement initiatives from Italy and the United Kingdom could inform efforts to routinely deliver best practice elsewhere:

**ITALY:** In 2011, investigators from Florence developed a database to monitor delivery of care for patients treated with tamoxifen and AIs, and those treated with AIs as first line therapy. This will enable evaluation of:

- Effectiveness of bisphosphonate therapy, particularly intravenous zoledronate.
- The impact of treatment on BMD, bone turnover markers and fracture rates.

**UNITED KINGDOM:** In 2007, investigators from London reported their experience with a software system to close the AI-induced osteoporosis care gap. The installation of a text recognition system on oncology department secretaries’ computers enabled automation of delivery of guideline-based care for patients undergoing treatment for breast cancer. Women aged between 50 and 80 years were automatically referred to an Osteoporosis Nurse Specialist for assessment and management. The software system automatically inserted text into the oncology department letters to the patients’ primary care physicians (PCP), advising the PCP that their patient would be receiving osteoporosis care. The PCPs of patients aged over 80 years were recommended to initiate osteoporosis treatment without undertaking a BMD test. Implementation of this system resulted in a 10-fold increase in the proportion of breast cancer patients referred for osteoporosis management.
GAP 3: DISEASES ASSOCIATED WITH OSTEOPOROSIS
There are many health problems which can increase an individual’s risk of developing osteoporosis and suffering fragility fractures. These include a broad array of disorders: autoimmune, digestive and gastrointestinal, endocrine and hormonal, hematologic, neurological, mental illness, cancer and AIDS/HIV. This report will focus on six common disorders: chronic obstructive pulmonary disease (COPD), diseases of malabsorption, rheumatoid arthritis (RA), primary or secondary hypogonadism, dementia and diabetes.

Chronic obstructive pulmonary disease

The World Health Organization (WHO) estimates that 65 million people have moderate to severe COPD worldwide. The two main types of COPD are chronic bronchitis and emphysema. Smoking is the primary cause of COPD, but up to a fifth of COPD may be attributable to occupational exposure to industrial pollutants and dust.

A systematic literature review established the average prevalence of osteoporosis among COPD sufferers to be 35%. Vertebral fractures, the most common fragility fracture, is of particular significance for patients with COPD. In such patients with already compromised lung function, a single vertebral fracture is estimated to reduce the vital capacity by 9%. Of additional concern is the observation that hip fracture sufferers who have COPD experience significantly increased post-hip fracture mortality. A study from the Veteran’s Affairs (VA) Health System in the United States reported that severe COPD patients had mortality at 12 months of 40%, compared to 31% in mild COPD and 29% in non-COPD subjects. Notably, this study also found that osteoporosis was known prior to the hip fracture for only 3% of participants, a care gap which has also been documented in the Netherlands.

In 2015, in response to the lack of specific guidelines for management of osteoporosis among COPD sufferers, a Dutch Working Group comprised of clinical experts in the field of COPD and fracture prevention published a 5-step approach which includes case finding, risk evaluation, differential diagnosis, therapy and follow-up.

Diseases of malabsorption

Celiac disease is one of the most common genetic disorders in the West and is estimated to affect 1% of the population in the United States. Worldwide, 5 million people live with Crohn’s disease and ulcerative colitis, conditions known as inflammatory bowel diseases (IBD).

Low bone mass is highly prevalent amongst sufferers of celiac disease and Crohn’s disease. Many factors contribute to this association: in Crohn’s disease these include intestinal resection and the resulting malabsorption of vitamin D and other nutrients, weight loss, chronic inflammation with increased levels of circulating cytokines, and frequent use of glucocorticoids. The major causes of osteoporosis amongst sufferers of malabsorption include malnutrition of calcium, vitamin D, protein and other nutrients, and the accompanying weight deficit. The incidence of fractures reported in a large study of celiac sufferers is elevated compared to non-sufferers, with increases of 90% and almost 80% for hip and wrist fractures, respectively. Similarly, the incidence of fracture among IBD sufferers is 40% higher than in the general population. Studies from Austria and the United States have reported that less than a quarter of IBD sufferers underwent BMD testing.

Clinical guidelines relating to the prevention and treatment of osteoporosis in celiac disease are available in Canada, Germany, the UK and the United States. Guidelines relating to the prevention and treatment of osteoporosis in inflammatory bowel disease (IBD) are available in the UK and IBD and other gastrointestinal diseases in the United States.

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) affects between 0.5% and 1% of adults in the developed world and resulted in about 49,000 deaths globally in 2010. The onset of RA most commonly occurs in women during their forties and somewhat later in men.

Sufferers of RA have lower BMD than healthy controls and the degree of bone loss observed is correlated with disease severity. Pro-inflammatory cytokines released into the circulation from the inflamed synovium are thought to cause the bone loss. A study undertaken with the British General Practice Research Database evaluated fracture incidence in more than 30,000 RA sufferers. As compared to a control group, the RA sufferers’ risk...
of hip fracture and vertebral fracture was increased 2-fold and 2.4 fold, respectively\textsuperscript{229}. Currently, RA is the only cause of secondary osteoporosis in the FRAX\textsuperscript{5} algorithm that is considered a predictor of fracture independent of bone density\textsuperscript{230}. RA sufferers frequently take GCs. Investigators in the VA Health System in the United States thus evaluated osteoporosis treatment among a cohort of 9,600 veterans with RA\textsuperscript{231}. Fewer than half had received preventive treatment for osteoporosis. Similar studies from Canada\textsuperscript{232, 233}, Finland\textsuperscript{234}, Germany\textsuperscript{235}, Mexico\textsuperscript{236}, South Korea\textsuperscript{237} and the United States\textsuperscript{238, 239} have also reported sub-optimal assessment and/or treatment of osteoporosis in RA sufferers.

Clinical guidelines which include the prevention and treatment of osteoporosis in RA are available in Brazil\textsuperscript{240}, Germany\textsuperscript{235}, South Africa\textsuperscript{241} and Spain\textsuperscript{242}. Furthermore, EULAR has produced internationally relevant guidance\textsuperscript{157}.

**Hypogonadism**

Hypogonadism describes a diminished functional activity of the gonads—the testes in males and ovaries in females—which results in diminished sex hormone biosynthesis. Hypogonadism presents in two forms:

**Primary hypogonadism:** Results from defects of the gonads e.g. Klinefelter’s syndrome in males and Turner syndrome in females.

**Secondary hypogonadism:** Resulting from hypothalamic or pituitary defects e.g. Kallmann syndrome in males and females, and anorexia in females.

The prevalence of hypogonadism has been estimated as 20% among men in their sixties and 30% among men in their seventies\textsuperscript{243}. In 2013, investigators from the United States used data from Clininformatics DataMart (CDM), which is one of the largest commercial health insurance populations, to examine androgen prescribing patterns in the United States during the period 2001 to 2011\textsuperscript{244}. Testosterone replacement therapy (TRT) use in men had risen to almost 4% of men in their sixties. Of particular concern was the observation that, of men newly prescribed TRT, only three-quarters had their serum testosterone level measured in the preceding 12 months (from 2001 through 2011). This assessment gap prompted production of a critical update of the 2010 Endocrine Society clinical practice guidelines for male hypogonadism\textsuperscript{245}. In relation to osteoporosis, the update to the guideline stated ‘… trials published since 2010 reinforce the positive effects of TRT on BMD and muscle strength, but the effects on the risk of fracture in men with osteoporosis remain unexamined.’

In 2015, the Italian Society of Endocrinology published guidelines on androgen replacement therapy in adult male hypogonadism\textsuperscript{246}. This guideline stated that ‘… testosterone supplementation should be combined with currently available treatments for individuals at high risk for complications, such as those with osteoporosis and/or metabolic disorders.’

**Dementia**

In December 2013, the first G8 Dementia Summit was convened in London, UK. Alzheimer’s Disease International (ADI) provided a policy brief for heads of government attending the Summit\textsuperscript{142}. The estimated number of people living with dementia in 2013 was estimated to be 44.4 million, a figure set to increase to 75.6 million and 135.5 million by 2030 and 2050, respectively. The largest increases in the projected number of dementia sufferers will be in East Asia and Sub-Saharan African regions. By 2050, the proportion living in what are currently low and middle income countries will increase to 71%, compared to 62% in 2013. In 2010, the global societal cost of dementia was US$604 billion, representing 1% of global GDP\textsuperscript{248}, and 486,000 people died as a result of dementia worldwide\textsuperscript{227}.

A significant overlap exists between sufferers of dementia and older people at high risk of injurious falls and fractures; this is particular evident amongst patients presenting with hip fracture. A UK study published in 2009 found that during a 12 month period, 66% of participants with dementia had a fall compared with 36% of age-matched controls\textsuperscript{249}. Furthermore, the incidence of falls in dementia was nine times higher than that observed among a control group. The incidence of hip fracture among patients with Alzheimer’s disease has been reported to be almost three times higher than amongst cognitively healthy peers.

Alzheimer’s disease has been reported to be almost three times higher than amongst cognitively healthy peers\textsuperscript{250}. In a meta-analysis, the prevalence of dementia amongst older hip fracture patients was estimated to be 19%\textsuperscript{251}. In 2007, the Scottish Hip Fracture Audit reported on the prevalence of dementia amongst hip fracture patients\textsuperscript{252}. Over a quarter (28%) of patients had a documented
past medical history of dementia, which the authors indicated was likely to be a significant underestimate of actual prevalence on account of the poor diagnosis rates for dementia documented at that time.

In 2011, a monograph on the subject of dementia, falls and fractures summarised the current evidence:

- Persons with dementia suffer more falls, more fractures and higher post-fracture mortality than those without dementia, yet they are under-assessed for falls risk factors and are less likely to receive treatment for osteoporosis.
- Falls and fracture patients have a high prevalence of dementia and cognitive impairment, yet do not routinely receive cognitive assessment and, consequently, frequently miss an opportunity for a diagnosis of dementia to be made.

Subsequent studies from Canada, Finland, UK and the United States have added to the evidence that osteoporosis is infrequently diagnosed and treated in people living with dementia. As illustrated in this section of the current report, guidelines have been developed for management of osteoporosis in several diseases where osteoporosis is a common comorbidity. As the population of dementia sufferers is set to grow spectacularly in the coming decades, evidence-based guidelines for the management of osteoporosis - and falls risk - in dementia must be drafted and implemented as soon as possible.

Diabetes

In 2015, the International Diabetes Federation (IDF) estimated that there were 415 million adults aged 20 to 79 years with diabetes worldwide, including 193 million who are undiagnosed. Data were not available to report the precise proportion of type 1 and type 2 diabetes globally. However, in high-income countries approximately 87% to 91% of all people with diabetes are estimated to have type 2 diabetes. Diabetes was estimated to have caused 5 million deaths and have cost between US$673 billion and US$1,197 billion in healthcare spending. Left unchecked, IDF estimates that by 2040 there will be 642 million people living with the disease.

Evidence is growing to suggest that diabetes and osteoporosis share pathophysiological mechanisms. The osteoblast-specific secreted protein, osteocalcin (OC), has been shown in animal studies to influence bone metabolism, glucose metabolism and fat mass, though the role in humans remains unknown. Individuals with type 2 diabetes have increased fracture risk, up to three times greater than that of non-diabetics for hip and other non-vertebral fractures. Why this should be so is not completely understood because there is strong evidence of normal to high BMD at both the hip and spine in type 2 diabetics.

In 2016, Bouxsein and colleagues published a comprehensive review on skeletal fragility in type 2 diabetes which provides several important take home messages:

- Despite often having normal to high BMD, individuals with type 2 diabetes have increased fracture risk irrespective of sex, race or ethnicity. Accordingly, BMD measurements may underestimate skeletal fragility in type 2 diabetics.
- There is little data available on the optimum management of osteoporosis in type 2 diabetics.
- In the absence of evidence to the contrary, management should adhere to the established principles of management of postmenopausal osteoporosis.

Given the scale of the threat posed to public health by diabetes, self-evidently, efforts to prevent the disease must be a priority for health systems worldwide. However, in light of the staggering number of individuals already affected, evidence-based guidelines for the management of osteoporosis in type 2 diabetes must be drafted and implemented as soon as possible.
GAP 4: PRIMARY FRACTURE PREVENTION FOR INDIVIDUALS AT HIGH RISK OF FRACTURE
As discussed in Gap 1 of this report, there is an enormous amount of work to be done to close the secondary fracture prevention care gap worldwide. IOF is of the firm belief that secondary prevention is the single most important, immediate mechanism to directly improve patient care and reduce spiraling fracture related healthcare costs. The ultimate goal in the longer term would be the prevention of the first fracture, and advances in fracture risk assessment during the last decade provide a platform for development of clinically effective and, crucially, cost-effective approaches.

In order to ensure that a primary fracture prevention programme has the potential to be cost effective, consideration must be given to which first fragility fracture is to be prevented. Primary prevention of hip fracture is likely to be more cost-effective than primary prevention of wrist fracture, because hip fractures cost considerably more to manage than wrist fractures. In this regard, consideration must be given to what proportion of all hip fractures occur as an individual’s first fragility fracture at any skeletal site, as illustrated in the Venn diagram in figure 4.

Whilst definitive data to populate such an analysis are not available, the following illustration is consistent with the current evidence-base:

- Approximately 50% of hip fracture patients have suffered clinically apparent fragility fracture(s) prior to breaking their hip, which was usually a non-vertebral fracture273,40.
- Conservative interpretation of studies from Spain and Japan suggests that a further 10%269 to 25%270 of hip fracture patients may have suffered previous vertebral fractures – the majority of which are not recognised or diagnosed as such271 – but have not suffered clinically apparent non-vertebral fractures.
- Therefore, 25-40% of hip fracture patients may have suffered the hip fracture as their first overt fragility fracture at any skeletal site.

This analysis highlights the challenge faced by efforts to pro-actively case-find the relatively small proportion of individuals who are likely to suffer a hip fracture as their first fragility fracture. It should also be noted that fragility fractures at sites other than the hip impose a significant burden on older people. Vertebral fractures lead to many adverse consequences for sufferers, including277:

- Back pain, loss of height, deformity, immobility and increased number of hospital bed days273, 274.
- Reduced quality of life resulting from loss of self-esteem, distorted body image and depression275-278.
- A significant negative impact on activities of daily living278, 280.

Studies from Australia281, Canada282 and the international Global Longitudinal Study of Osteoporosis in Women (GLOW)283 have all reported significant reductions in health-related quality of life among individuals who have suffered fragility fractures at all skeletal sites. Accordingly, a robust clinical case exists for primary prevention of all major osteoporosis fractures, defined as hip, clinical vertebral, wrist or proximal humerus fractures. Pragmatic approaches to case-finding individuals at high risk of suffering these fractures as their first fracture include:

- Gap 2: Osteoporosis induced by medicines: Systematic case-finding of individuals at high fracture risk in this group.
- Gap 3: Diseases associated with osteoporosis: Systematic case-finding of individuals at high fracture risk in this group.
- Absolute fracture risk calculation: Systematic application of tools such as FRAX® to risk stratify the older population.

The SCOOP trial, which is currently ongoing in the UK, will provide valuable insights on primary fracture prevention strategies284. This pragmatic, randomised controlled trial (RCT) is following more than 12,000 women aged 70 to 85 years over a five-year period. The study will assess the effectiveness and cost-effectiveness of a community-based screening programme which utilises the FRAX® algorithm and BMD measurement to assess 10-year probability of fracture.

Information specifically concerned with the extent of the primary fracture prevention care gap is not available. Given the pervasive and persistent secondary fracture prevention care gap documented in Gap 1, it would be reasonable to assume that the primary fracture prevention care gap among high risk individuals is at least as wide. While not specific to primary fracture prevention, information regarding national use of FRAX® and national prescribing levels provide an indication of overall assessment and treatment rates within a country. Importantly, a major report on osteoporosis in the European Union (EU) published in 2013 revealed that for the 12 month period from November 2010 to November 2011 uptake of FRAX® was sub-optimal in all EU countries, including those for which FRAX®

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**Figure 4. Distribution of prior fracture history among hip fracture patients**

**Individuals who suffered a hip fracture as their FIRST fragility fracture**

- Individuals who suffered a hip fracture after previous vertebral fracture(s)
- Individuals who suffered a hip fracture after both types of previous fracture(s)
- Individuals who suffered a hip fracture after previous non-vertebral fracture(s)
More recent information on the usage of FRAX® is illustrated in figure 5. The 2013 EU report also documented national prescribing levels. These data, in combination with an algorithm which calculated the number of patients who were eligible for treatment in each of the 27 EU member states at the time, enabled estimation of the potential treatment gap for each country in 2010. This approach assumed that all those treated were actually eligible for treatment and not at a lower level of risk, so may have underestimated the treatment gap among high risk patients. In total in the EU, 10.6 million out of 18.4 million women who were eligible received treatment. Among men, 1.7 million men out of the 2.9 million men who were eligible received treatment. The inferred treatment gaps for each EU member state are illustrated for women and men in figure 6.

Most clinical guidelines cover both secondary fracture prevention and primary fracture prevention. A notable exception is guidance from NICE in the UK, which first published guidance specifically on primary fracture prevention in 2008 to complement existing secondary prevention guidance.

Several health systems have implemented systematic approaches to primary fracture prevention targeted at high risk individuals in parallel to secondary prevention efforts. The Kaiser Permanente Healthy Bones Program and Geisinger Health System HI-ROC Program provide high-performing examples of this approach.

Figure 6. The EU osteoporosis treatment gap in 2010.
GAP 5: THE IMPORTANCE OF STAYING ON TREATMENT
The focus of this report thus far has been upon care gaps which result in individuals at high risk of fragility fracture not undergoing assessment and/or not receiving osteoporosis treatment. This section considers a different, but common challenge in the chronic disease arena: ensuring that individuals who are initiated on treatment actually stay on treatment.

Two measures of adherence to treatment are commonly used in studies:

- **Persistence**: Defined as either the time to treatment discontinuation or as the proportion of patients that at a certain time point still fill prescriptions without a gap in refills longer than an allowed period of time (e.g. 30, 60 or 90 days).

- **Compliance**: Defined as the ability of a patient to adhere to the dosing, timing and conditions described by the prescriber or in accordance with the medicine’s patient information leaflet. One measure of compliance is the medication possession ratio (MPR). MPR is usually defined as the number of days of medication available to the patient, divided by the number of days of observation.

In routine clinical practice, both persistence and compliance with osteoporosis treatment are sub-optimal, a phenomenon previously reported for other classes of widely-used medicines including antihypertensives and statins. Approximately half of patients initiated on osteoporosis treatment do not follow their prescribed treatment regimen and/or discontinue treatment within a year. This is particularly notable on account of the flexibility of dosing options of widely available osteoporosis treatments, which can be taken as daily, weekly or monthly tablets, or as daily, quarterly, six-monthly or annual injections. Intravenous or sub-cutaneous routes of administration provide a means to ensure 100% adherence with treatment, as long as a robust system is in place to administer the initial injection and reliably arrange follow-up injections at appropriate intervals. It has been estimated that improved adherence in the United States would reduce fracture rates by 25%, equating to approximately 300,000 fewer fractures per year and generate savings of US$3 billion.

In 2013, the Medication Adherence and Persistence Special Interest Group of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) undertook a systematic literature review of interventions to improve osteoporosis medication adherence. Interventions identified which may improve adherence were:

- Simplification of dosing regimens
- Electronic prescriptions
- Patients decision aids
- Patient education

Patients were most persistent with medications which had the least frequent dosing regimens. The use of electronic prescriptions in combination with verbal counselling was associated with a 2.6-fold improvement in short-term compliance compared to verbal counselling alone. A study from the United States evaluated use of a patient decision aid in combination with usual primary care practice compared to usual primary care practice alone. While adherence at 6 months was similar for both groups, the proportion with more than 80% adherence was significantly higher with the decision aid. With regard to the impact of patient education, it should be noted that the largest and least biased studies reviewed showed only marginal improvement in adherence.

The impact of FLS on adherence has been evaluated in several studies. Among patients managed by an FLS after fracture, between 74% and 88% remained on treatment at 12 months, and between 64% and 75% at 24 months. These data reinforce the notion that a “teachable moment” exists after individuals have suffered a fragility fracture which can be capitalized upon by an FLS to improve adherence to treatment. The FLS team at Concord Hospital in Sydney, Australia also compared adherence among patients initiated on treatment by the FLS who were subsequently followed up by either the FLS or local primary care physicians. Notably, persistence at 24 months was similar in both groups leading the investigators to conclude that the main function of an FLS is to initiate a management plan for osteoporosis after fractures occur. If effective communication between the FLS and local PCPs is established, PCPs are well-placed and willing to manage osteoporosis care in the long term after initial recommendations are provided by the FLS.
GAP 6:
PUBLIC AWARENESS OF OSTEOPOROSIS AND FRACTURE RISK
In recent years, a number of studies have been undertaken to characterise awareness of osteoporosis and fracture risk among older people. In 2008, investigators from a non-profit Health Maintenance Organization (HMO) in the Northwest United States sought to evaluate key stakeholder perspectives on osteoporosis care after a fracture\textsuperscript{108}. These stakeholders included fracture patients, quality and other healthcare managers, PCPs, and orthopaedic clinicians and staff. Both patients and PCPs commented that confusion of osteoporosis with osteoarthritis was common. Furthermore, this confusion led to the perception that osteoporosis is a benign consequence of ageing.

In 2010, Canadian investigators evaluated osteoporosis knowledge among older fracture patients who were treated by orthopaedic surgeons at two major teaching hospitals in Ontario\textsuperscript{309}. Fracture patients were asked two questions:

1. Do you know what osteoporosis is?

2. If Yes, what do you think it is?

The overwhelming majority of respondents (91\%, 115/127) said that they knew what osteoporosis was. Among these individuals, 75\% gave responses that were considered to be correct. Individuals who had reported a diagnosis of osteoporosis or a higher education level were more likely to provide a correct definition, however, the odds reduced with age. Almost 40\% of the interview participants completed a 'Facts on Osteoporosis Quiz'. Notably, less than half (41\%) of those who took the quiz knew that a person who had suffered a spine fracture was at increased risk of suffering a fracture in the future as compared to a fracture-free individual.

The acute rehabilitation setting could provide an opportunity to improve post-fracture osteoporosis treatment. In this setting, investigators from Boston in the United States assessed fracture patients’ willingness to participate, free of charge, in a secondary fracture prevention programme\textsuperscript{310}. Less than half of eligible patients chose to participate, with reluctance to take another medication cited as the most common reason for not doing so.

In New Zealand, patients’ and doctors’ perceptions of appropriate intervention thresholds for fracture risk have been surveyed\textsuperscript{311}. Stark differences were evident. An absolute risk of 50\% for both major osteoporotic and hip fractures was identified by patients as meriting drug treatment, as compared an absolute risk of 10\% among doctors. Further, patients determined that an effective drug would achieve a relative risk reduction of 50\%. On this basis, patients in New Zealand would consider taking treatment for osteoporosis only when the absolute reduction in fracture risk was 25\%.

The international GLOW study has compared self-perception of fracture risk with actual risk among more than 60,000 postmenopausal women in 10 countries in Europe, North America, and Australia\textsuperscript{312}. Key findings included:

- Among women reporting a diagnosis of osteopenia or osteoporosis, only 25\% and 43\%, respectively, thought their risk was increased.

- Among women whose actual risk was increased based on the presence of any one of seven risk factors for fracture, the proportion who recognized their increased risk ranged from 19\% for smokers to 39\% for current users of glucocorticoid medication.

- Only 33\% of those with at least 2 risk factors perceived themselves as being at higher risk.

These studies are illustrative of the evidence base relating to awareness of fracture risk among older people. The findings of some studies are in conflict with others. Knowledge gaps are evident among some groups but not others. Efforts to improve awareness need to provide clear, evidence-based messages. Disease awareness campaigns (DACs) such as 2Million2Many from the NBHA in the United States provide an innovative example of implementing this approach\textsuperscript{106}. The key messages for 2Million2Many are very simple and compelling:

- Every year, there are 2 million bone breaks that are no accident (in the USA).

- They are the signs of osteoporosis in people as young as 50.

- But only 2 out of 10 get a simple follow-up assessment.

- Together we can break osteoporosis before it breaks us. But we must speak up. Remember: Break a bone, request a test.

The impact of the 2Million2Many campaign cannot be assessed in isolation, because pursuant to the launch of this campaign in 2012, NBHA and NOF launched a major FLS implementation initiative in 2013\textsuperscript{137} and a Qualified Clinical Data Registry focused on outcomes in osteoporosis and post-fracture care in 2014\textsuperscript{86}. In 2015, the National Committee on Quality Assurance (NCQA) published a report on post-fracture osteoporosis care for women for the period 2007 to 2014\textsuperscript{313}. Together these initiatives resulted in a significant improvement in post-fracture care in the United States.

An initial focus of DACs should be to drive awareness throughout the population of the world that fracture begets fracture. If all individuals aged 50 years or over knew that suffering a first fragility fracture significantly increases their risk of suffering second and subsequent fractures, up to one half of all people who will suffer hip fractures in the future could be aware of that risk, and be proactive in taking steps to lower it.
GAP 7: PUBLIC AWARENESS OF BENEFITS VERSUS RISKS OF OSTEOPOROSIS TREATMENT
Numerous RCTs and Cochrane Collaboration systematic reviews have demonstrated the efficacy and safety of treatments for osteoporosis. However, in the last decade use of these treatments among individuals at high risk of fracture has been significantly impacted by reports relating to rare side effects, including osteonecrosis of the jaw (ONJ), atrial fibrillation (AF) and atypical femur fracture (AFF). The importance of vigilant monitoring of the occurrence of side effects cannot be overstated. That being said, the benefits of anti-osteoporosis therapies for the prevention of fragility fractures in high risk individuals significantly outweigh harm potentially attributable to these medicines.

ONJ has primarily been observed among patients taking high doses of bisphosphonates for treatment of bone metastases rather than osteoporosis. It is very rare in the context of treatment for osteoporosis. In fact, Swedish investigators estimated that an average Swedish dental practice (of 1,234 patients) would encounter one osteoporosis patient with new oral bisphosphonate-related ONJ every 62nd year. In 2015, an International Task Force estimated the incidence of ONJ in the osteoporosis population to be 0.001% to 0.01%, which was marginally higher than the incidence observed in the general population of <0.001%.

With regards to atrial fibrillation, an increase in risk was observed for zoledronic acid infusions compared to placebo in the HORIZON-PFT Trial (1.3% vs. 0.5%, p<0.001). However, a meta-analysis of 26 RCTs of oral bisphosphonates reported no increase in risk of AF.

The occurrence of AFF has also been the subject of considerable debate within the media. Current estimates suggest that atypical fractures occur in 3 to 50 cases per 100,000 person years for bisphosphonate users. Investigators from Kaiser Permanente in the United States analysed a large population of bisphosphonate users to explore the relationship between duration of therapy and risk of AFF. Age-adjusted incidence rates for an AFF were 1.78 per 100,000 person years (95% confidence interval [CI], 1.5-2.0) with exposure from 0.1 to 1.9 years, which increased to 113.1 per 100,000 person years (95% CI, 69.3-156.8) with exposure from 8 to 9.9 years. The authors concluded that the incidence of AFF increases with longer duration of bisphosphonate use, but this risk should be counterbalanced with the proven benefits in terms of fracture reduction.

In 2016, the impact of US Food and Drug Administration (FDA) safety-related announcements on the use of bisphosphonates after hip fracture was the subject of a short report. A large sample of hip fracture patients insured by United HealthCare were analysed. Overall, the proportion of hip fracture patients treated with bisphosphonates after their hip fracture occurred declined from 15% in 2004 to 3% in the last quarter of 2013. A significant decline in bisphosphonate prescribing was observed after the 2007 FDA announcement relating to AF, which continued after the 2010 FDA announcement relating to atypical fractures. The authors concluded that given the clinical importance of the secondary prevention of hip fracture, these results highlight the need to weigh benefits versus harms of bisphosphonates and to improve the communication of drug safety information with both clinicians and patients.

This is the crux of this issue, and demonstrates a failure to counter adverse coverage of rare side effects of osteoporosis treatments across media platforms. The risk-benefit calculation for treatment of osteoporosis among individuals who are at high risk of suffering fragility fractures, including life changing and life threatening hip fractures, significantly favours treatment. Clinicians and patients need to be able to objectively discuss and evaluate the risk benefit calculation for the patient’s individual circumstances when making collaborative treatment decisions. Having ready access to absolute fracture risk calculation tools such as FRAX can make such discussions far more tailored – and meaningful - to individual patients. It requires all those involved in the care of osteoporosis patients to ensure clear, balanced communication of these issues both to individual patients and more widely when opportunities arise.
GAP 8: ACCESS AND REIMBURSEMENT FOR OSTEOPOROSIS ASSESSMENT AND TREATMENT
During this decade, IOF has undertaken a series of regional audits throughout the world\textsuperscript{10, 324-329}. These audits have evaluated epidemiology, costs and the burden of osteoporosis in the regions, and have included an overview of access and reimbursement to treatment. A summary is provided for each region below. With regard to the current situation in North America, Osteoporosis Canada and the National Osteoporosis Foundation in the United States have provided summaries.

**Asian-Pacific**

The most recent IOF Asia-Pacific Regional Audit was published in 2013\textsuperscript{324}. The audit noted that reimbursement varied greatly across the region, ranging from zero to 100% reimbursement for the most commonly prescribed medications. There were also differences between public and private insurance, with only partial reimbursement being offered, or restrictive criteria applied, such as age or history of prior fracture.

Access to BMD testing can also have a significant impact on access to osteoporosis treatment. In this regard, the audit noted that many countries were seriously under-resourced in terms of DXA scanners. Further, BMD testing is not fully reimbursed in many countries, which serves as another barrier to accessing treatment.

**Eastern Europe and Central Asia**

The IOF Eastern European and Central Asian Regional Audit was published in 2010\textsuperscript{10}. Throughout the region availability and access to osteoporosis treatment was extremely limited. In the Russian Federation, while treatment was free of charge for individuals with severe osteoporosis, salmon calcitonin was the only treatment available.

In most countries, BMD testing was only accessible in the main cities, yet in about one-third of the countries, more than 40% of the population resides in a rural area. Further, in countries without reimbursement, the majority of the population cannot afford DXA examinations.

**European Union**

In 2013, IOF and the European Federation of Pharmaceutical Industry Associations (EFPIA) undertook a comprehensive audit of the EU member states at the time\textsuperscript{10, 326, 327}. While most treatments were reimbursed in most countries, full reimbursement was provided in only 7 member states. In the remaining countries, the level of reimbursement varied from zero in Malta, up to 100% for selected treatments in Luxembourg and Spain.

As illustrated in figure 7, access to BMD testing varied dramatically across the continent. The survey found that about half of countries in the EU had the recommended number of DXA scanners to adequately serve their populations. However, given that information was not available on the specific use of these scanners (i.e. for routine clinical service provision or for research purposes), or levels of staffing in DXA units, it is likely that a majority of countries did not have adequate access to BMD testing to implement national clinical guidelines for osteoporosis.

**Latin America**

The IOF Latin American Regional Audit was published in 2012\textsuperscript{328}. Bisphosphonates were widely available throughout the region with considerable variability in reimbursement policy. Other osteoporosis therapies such as selective estrogen receptor modulators (SERMs), parathyroid hormone analogues (PTH), hormone replacement therapy (HRT), and strontium ranelate were also available, but access was often restricted.

Access to BMD testing was limited to urban areas throughout the region with availability estimates ranging from 1 to 10 devices per 1 million inhabitants.

**Middle East and Africa**

The IOF Middle East and Africa Regional Audit was published in 2011\textsuperscript{329}. The situation documented in this region was very heterogeneous. Some countries had a very good reimbursement policy for diagnostic tools and therapies, while in other countries there was absolutely no reimbursement available and patients had to pay for all diagnostic tests and treatment.

**North America**

In Canada there is no single national healthcare system. Healthcare falls under the independent jurisdiction of each of the 10 provinces and 3 territories. There is reimbursement for many of the oral bisphosphonates in all Canadian provinces for seniors who are indicated for such treatment. However, coverage for other osteoporosis medications such as denosumab and zoledronic acid is quite variable depending on the province/territory.

In the United States reimbursement for treatment varies greatly depending on each patient’s health plan. Health care reform is evolving from fee for service to supporting improved quality, prevention and care coordination with financial incentives (or penalties) to encourage healthcare professionals and health systems to report on and improve patient outcomes. There are a number of quality measures focused on osteoporosis and post-fracture care but performance around these measures remain low compared to other major chronic diseases. Further, a major drop in reimbursement for DXAs performed in the office setting has led to a drop in the number of providers and more than 1 million less DXAs performed.

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**Figure 7. Access to DXA scanners in the EU in 2010\textsuperscript{326}**

n.b. DXA units per million of the general population in 2010 based on sales of DXA in the EU supplied by manufacturers. The horizontal line denotes a minimum service requirement\textsuperscript{319}.

Adapted from Arch Osteoporos (2013) 18:144 Kanis JA et al. with permission from Springer.
GAP 9: PRIORITIZATION OF FRAGILITY FRACTURE PREVENTION IN NATIONAL POLICY
The IOF regional audits provide comprehensive information on the level of priority afforded to fragility fracture prevention by governments throughout the world\textsuperscript{10, 324-329}.

Asia-Pacific

The most recent IOF Asia-Pacific Regional Audit was published in 2013\textsuperscript{324}. At the time, the governments of just 4 of the 16 countries represented in the audit had designated osteoporosis as a national health priority: Australia (2002), Chinese Taipei (2005), Singapore (2009) and China (2011). Since 2013, significant progress has also been made in New Zealand\textsuperscript{112}.

Eastern Europe and Central Asia

The IOF Eastern European and Central Asian Regional Audit was published in 2010\textsuperscript{325}. At the time, of the 21 countries presented in the audit, only 2 (Republic of Belarus and Bulgaria) considered osteoporosis as a health priority.

European Union

As illustrated in the IOF-EPFIA Audit 2013\textsuperscript{10, 326, 327}, the majority of member states (18/27) did not recognize osteoporosis or musculoskeletal diseases as a national health priority (NHP). Of those member states that had developed a NHP, the focus was on nutrition (6 countries), falls prevention (4 countries), exercise (4 countries) and the implementation of FLS (2 countries).

Latin America

The IOF Latin America Regional Audit 2012\textsuperscript{328} showed that osteoporosis was a NHP in only 3 of the 14 countries in the audit: Brazil, Cuba and Mexico. Although osteoporosis guidelines were available in 9 of the 14 countries, they were only government endorsed in Bolivia and Cuba.

Middle East and Africa

The IOF Middle East and Africa Regional Audit 2011\textsuperscript{329} found that osteoporosis was considered a health priority in only 3 out of the 17 countries included in this audit: Iran, Iraq and Jordan. Osteoporosis guidelines were endorsed by governments in Egypt, Lebanon and South Africa, with approval pending for guidelines in Iran and Iraq.

North America

Healthcare in Canada falls under the independent jurisdiction of each of the 10 provinces and 3 territories. There is therefore no national governmental policy on osteoporosis or fracture prevention. However, Osteoporosis Canada (OC) is actively promoting implementation of effective FLS as a priority. OC will soon be launching an FLS Registry to showcase Canadian FLS meeting all 8 of the \textit{Essential Elements for Fracture Liaison Services}\textsuperscript{331}.

In the United States, despite a landmark report by the Surgeon General in 2004\textsuperscript{2} and the specific recommendations from key national and scientific societies\textsuperscript{132,133,134} intended to prioritize and improve osteoporosis and fracture prevention, implementation has been poor. Many patients are not given the necessary information about prevention and are not receiving appropriate testing to diagnose osteoporosis or establish osteoporosis risk. Most importantly, a majority of patients who have osteoporosis-related fractures are not being diagnosed with osteoporosis and are not receiving any of the Food and Drug Administration (FDA)-approved, effective therapies.
GAP 10: THE BURDEN OF OSTEOPOROSIS IN THE DEVELOPING WORLD
Asia-Pacific

There is an urgent need at the national level to accurately quantify osteoporosis and fracture prevalence in many countries of this region. India will become the most populous country in the world in the next few decades, and life expectancy of Indians is set to increase considerably. In 2013, a study of the incidence of hip fracture in the Rohtak district of North India found that among individuals aged 50 years or over, the crude incidence was 159 per 100,000 in women and 105 per 100,000 in men. Application of these rates to the United Nations Population Projection for India for 2015 suggests that the number of hip fractures in men and women in 2015 was 121,000 and 185,000 cases, respectively. Efforts by the Indian Society for Bone and Mineral Research (ISBMR) to conduct multicentre, large-scale hip fracture incidence studies will provide robust fracture epidemiology to inform policy development. The IOF Asia-Pacific Regional Audit 2013 also reported a paucity of fracture data for Malaysia, Pakistan, Sri Lanka, Thailand and Vietnam.

Eastern Europe and Central Asia

In 2010, the IOF Eastern European and Central Asian Regional Audit stated: So the under recognition of osteoporosis on the part of governments and healthcare professionals in the region is mainly due to the lack of solid epidemiological and economic data on the costs and burden of the disease. In 2012, work undertaken to inform development of a FRAX® model for the Russian Federation provided estimates of fracture incidence for Russia. The total number of hip fractures estimated to have occurred in 2010 (112,000) was expected to rise to 159,000 in 2035. The estimated number of major fractures was expected to rise from 590,000 to 730,000 over the same time interval. The investigators highlighted that these estimates were based on extrapolation of robust fracture information collected in Yaroslavl and Pervouralsk to the entire population of the Russian Federation. Multi-centre, large-scale epidemiological studies should be undertaken in Russia and other countries in the region to inform policy development.

Latin America

The IOF Latin American Regional Audit identified a major lack of data on fracture incidence in the region in 2012. Only 8 of the 14 countries in the audit had published hip fracture incidence data, and many of the studies were out-dated and non-population based. Further, there were virtually no data available on the status of vertebral fractures in 8 of the 14 audited countries. In 2015, work undertaken to inform development of a FRAX® model for Brazil provided estimates of hip fracture incidence for Brazil. There were estimated to be 80,640 hip fractures in 2015, of which 23,422 were in men and 57,218 in women. In 2040, the number of hip fractures was expected to rise to 55,844 in men and 141,925 in women, a rise of 238 and 248 %, respectively.

Middle East and Africa

The IOF Middle East and Africa Regional Audit identified a major lack of data on fracture incidence in the region in 2011. Only 6 of the 17 countries in the audit had published hip fracture incidence data. Further, prevalence rates for vertebral fractures were available for only 3 countries.

All references included in this report are available at the following link: www.worldosteoporosisday/2016-report/references
CALL TO ACTION

The ten care gaps described in this report, together with their associated solutions, provide a new Global Framework for tackling the impending catastrophic burden that will be placed on the world’s population and economy by fragility fractures. At the national level policymakers, healthcare professionals’ organisations and national osteoporosis societies can use this framework to identify local gaps in the provision of best practice for the populations that they serve. Where currently absent, development of national strategies to close these gaps can be informed by the numerous international examples of clinical guidelines and quality improvement initiatives which have been highlighted in this report. It must be emphasised that this document is not an end in itself, but is instead best viewed as a call to action. The solutions to many of the problems we face have been identified and at least partly implemented, but not yet fully at a sufficient level to impact the approaching fracture tsunami. In the words of Leonardo da Vinci, “Knowing is not enough. We must apply. Being willing is not enough. We must do.” The time for optimal management of bone health is now.