List of supplementary material

Supplementary File 1 - Interview guide

Objective

The objective of the study for which we are conducting this interview is to evaluate the costs associated with the use of the REMS approach for the diagnosis of osteoporosis compared to the gold standard (DXA) from the perspective of the National Health Service through a cost-minimization analysis.

Professional information

We would like to start the interview by asking you some professional information. In particular, we would like to know:

- the role you currently hold;
- your affiliation;
- your experience in the management of patients with osteoporosis.

Target population

Recently published studies that evaluated the diagnostic and predictive ability of REMS technology compared to DXA (gold standard) involved the following populations: 1) postmenopausal women aged between 51 and 70 years (Di Paola et al, 2018); 2) women aged between 30 and 90 years (Cortet et al, 2021; Adami et al, 2020; Di Paola et al, 2018), 3) men aged between 30 and 90 years (Ciardo et al, SIOMMMS 2020) and 4) adolescents (Caffarelli et al. ICCBH, 2019).

1. In clinical practice, and in your experience, what is the target population for the REMS approach in the diagnosis of osteoporosis? Is it the same for DXA?
   1.1. Are there any differences?
   1.2. If so, why?

Diagnostic pathway

2. Could you explain to us how a diagnosis of osteoporosis is made using the REMS approach on axial anatomical sites? And with DXA? (*hint: from the interview with the patient to the examination and reporting*)
   2.1. In which setting(s) is the examination usually carried out with the REMS approach? And with DXA? (*hint: outpatient, day hospital, hospitalization, at home*)
   2.2. Are these exams followed by other instrumental exams? If so, which ones? Are they different depending on the initial approach adopted (REMS or DXA)?
3. Does the overall diagnostic pathway vary depending on the results obtained through the main instrumental examination (REMS or DXA)? If so, in what aspects?
   3.1. What is the impact of this result on the choice of the following therapeutic pathway? Is the impact different depending on whether the outcome derives from the REMS approach rather than DXA?
4. Based on your experience, what are the factors that most influence the choice between the two diagnostic approaches (REMS and DXA)? (*hint: clinical characteristics of the patient; type of patient - e.g. bedridden patient, pregnant woman, fractured patient, arthrosis, rare diseases; ease of use of the technology, safety, technology already present in the hospital; need to monitor the state patient's bone; waiting lists; etc.*)
   4.1. According to your experience, do you think there is a problem of accessibility of patients to REMS for the diagnosis of osteoporosis? What about DXA? For what reason(s)?
      4.1.1. If so, do you think this has a significant impact on the NHS's ability to identify patients at risk and make timely diagnoses?

4.2. In your experience, is there an instrumental examination (REMS or DXA) preferable in the following situations?
- Fracture
- Bedridden patient
- Bone degeneration (arthrosis, calcifications, or other)
- Prevention
- Diseases that increase the risk of developing osteoporosis
- Patient with high BMI
- Pregnancy

If so, which one? Is it just preferable or strongly recommended?

5. Once a diagnosis of osteoporosis has been established, what is the recommended frequency of repetition of the instrumental examination to monitor the progression of bone loss?
   5.1. Are there differences in timing depending on the approach adopted for the diagnosis (REMS or DXA)? If so, why?
   5.2. In your experience, does the frequency of the exam in real clinical practice reflect that recommended? If not, why?
   5.3. For follow-up instrumental examinations, is it important to maintain the same approach (REMS or DXA) adopted in the diagnosis or is it possible to change?
      5.3.1. Does the therapeutic pathway change depending on the instrumental examination performed in the follow-up? If so, in what aspects?

<u>Consumption of resources</u>

6. Is there a REMS equipment in your structure? What about DXA?
   6.1. If so, is there more than one (REMS and / or DXA)?
7. Who are the professionals involved in the diagnosis of osteoporosis through the REMS approach? And with DXA? (*hint: medical doctor, resident, radiology technician, nurse, other healthcare personnel*)
   7.1. Is it necessary to carry out special training for the use of REMS for the purpose of diagnosing osteoporosis? What about DXA for the purpose of diagnosing osteoporosis? If so, can you describe how it is done in the facility where you work?
8. For the purpose of diagnosing osteoporosis, does the use of REMS imply an involvement of administrative staff? If so, for which activities? And what about DXA?
9. What consumables are used for the execution of REMS for the purpose of diagnosing osteoporosis? What about DXA? (*hint: gloves, disinfectant, medical bed sheet, etc*.)
10. The SIOMMMS guidelines provide for carrying out some laboratory tests (level I and II*) that allow the differential diagnosis between primary and secondary osteoporosis and the evaluation of bone metabolism. Are these laboratory tests performed regardless of the instrumental examination performed (REMS or DXA) for the purpose of diagnosing osteoporosis? Or are there any differences?
    10.1. Based on your experience, what is the percentage of patients with a positive instrumental test for whom I and II level laboratory tests are performed?

** Level I exams: VES; complete blood count; Fractional protidemia; Calcemia; Phosphorea; Total alkaline phosphatase; Creatininemia; Calciuria of 24 h.*
Level II exams: Ionized calcium; TSH; Serum parathyroid hormone; Serum 25-OH-vitamin D; Cortisolemia after overnight suppression test with 1 mg dexamethasone; Total testosterone in males; Serum and/or urinary immunofixation; Anti-transglutaminase antibodies; Specific tests for associated pathologies (e.g. ferritin and % transferrin saturation, tryptase, etc.)
Level II exams are recommended when there is suspicion of secondary forms of osteoporosis and their choice must be based on the anamnestic and clinical evaluation of the individual patients.

Supplementary Table 1 - Sample description (expert elicitation exercise)

	Experts characteristics (n=13)
Professional figure, %	
Endocrinologist	15.4%
Gynecologist	15.4%
Internist	15.4%
Orthopedist	15.4%
Physiatrist	15.4%
Radiologist	7.7%
Rheumatologist	15.4%
Geographical region in which they operate, %	
North	38.5%
Centre	38.5%
South	23.1%
Nature of facility in which they operate, %	
Public	46.2%
Private	53.8%
Years of experience in managing patients with osteoporosis, mean (SD)	24.5 (10.4)

Supplementary Table 2 - Resource consumption – Number of professionals and time dedicated by each professional to the diagnosis of osteoporosis

Professional figure	Input	REMS mean (SD)			DXA mean (SD)		
		Most conservative scenario (L)	Base-case scenario (M)	Least conservative scenario (H)	Most conservative scenario (L)	Base-case scenario (M)	Least conservative scenario (H)
Clinician	# professionals	0.8 (0.4)	0.9 (0.3)	1.2 (0.4)	0.8 (0.4)	0.9 (0.3)	1.1 (0.3)
	Time dedicated (in minutes) - Patient interview	5.1 (2.8)	9.5 (4.5)	13.2 (6.6)	4.6 (4.3)	6.6 (6.6)	10.5 (9.0)
	Time dedicated (in minutes) - Exam execution	7.3 (3.9)	10.5 (4.3)	15.4 (7.2)	3.0 (5.4)	6.2 (7.4)	10.5 (9.8)
	Time dedicated (in minutes) - Reporting and communication of the outcome	5.8 (3.9)	10.2 (4.8)	14.5 (6.9)	6.1 (4)	9.3 (4)	13 (5.4)
	Time dedicated (in minutes) – Manual data elaboration	n.a.	n.a.	n.a.	3.0 (4.8)	5.5 (6.4)	8.0 (8.9)
Nurse	# professionals	0.2 (0.4)	0.2 (0.4)	0.5 (0.5)	0.5 (0.5)	0.6 (0.5)	0.6 (0.5)
	Time dedicated (in minutes) - Patient interview	1.2 (2.2)	1.4 (2.2)	1.5 (2.4)	2.8 (4.1)	3.4 (4.6)	5.5 (5.5)
	Time dedicated (in minutes) - Exam execution	1.9 (4.3)	2.3 (4.8)	3.5 (8.5)	3 (4.2)	3.7 (4.9)	5.0 (7.1)
	Time dedicated (in minutes) - Reporting and communication of the outcome	0.8 (1.9)	1.2 (3.0)	1.2 (3.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Time dedicated (in minutes) – Manual data elaboration	n.a.	n.a.	n.a.	0.5 (1.6)	0.5 (1.6)	0.5 (1.6)
Radiology technician	# professionals	0.2 (0.4)	0.3 (0.5)	0.3 (0.5)	0.9 (0.3)	0.9 (0.3)	1.0 (0.0)
	Time dedicated (in minutes) - Patient interview	0.8 (1.9)	1.4 (3.0)	2.3 (4.8)	5.6 (3.5)	8.1 (5.7)	12.3 (6.5)
	Time dedicated (in minutes) - Exam execution	1.5 (3.2)	2.7 (5.3)	3.5 (6.9)	10 (4.7)	15.7 (3.9)	21.5 (5.8)
	Time dedicated (in minutes) - Reporting and communication of the outcome	0.4 (1.4)	0.8 (2.8)	1.2 (4.2)	1.5 (3.4)	2.0 (4.2)	2.5 (5.4)
	Time dedicated (in minutes) – Manual data elaboration	n.a.	n.a.	n.a.	5.5 (5.0)	9.0 (6.1)	12.5 (9.8)
Resident	# professionals	0.2 (0.4)	0.3 (0.5)	0.5 (0.7)	0.3 (0.5)	0.5 (0.5)	0.5 (0.5)
	Time dedicated (in minutes) - Patient interview	1.2 (2.2)	2.2 (3.8)	2.7 (4.8)	1.6 (2.4)	2.6 (3.5)	5 (6.2)
	Time dedicated (in minutes) - Exam execution	1.9 (3.3)	3.1 (5.2)	4.6 (7.8)	2 (4.8)	4.2 (6.6)	6 (8.4)
	Time dedicated (in minutes) - Reporting and communication of the outcome	0.9 (2.8)	1.4 (3.0)	2.3 (4.8)	1.6 (3.3)	2.3 (4.8)	3.5 (6.7)
	Time dedicated (in minutes) – Manual data elaboration	n.a.	n.a.	n.a.	2.0 (4.8)	3.5 (6.7)	5.0 (8.5)
Other healthcare personnel	# professionals	0.0 (0.0)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.3 (0.5)	0.4 (0.7)
	Time dedicated (in minutes) - Patient interview	0.0 (0.0)	0.0 (0.0)	0.1 (0.3)	0.1 (0.3)	1.1 (3.1)	2.0 (4.8)
	Time dedicated (in minutes) - Exam execution	0.0 (0.0)	0.4 (1.4)	0.8 (2.8)	0.5 (1.6)	1.0 (3.2)	1.5 (4.7)
	Time dedicated (in minutes) - Reporting and communication of the outcome	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (2.1)	1.0 (2.1)	2 (4.8)
	Time dedicated (in minutes) – Manual data elaboration	n.a.	n.a.	n.a.	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Administrative staff	# professionals	0.5 (0.5)	0.5 (0.5)	0.6 (0.5)	0.9 (0.3)	1.3 (0.5)	1.8 (1.1)
	Time dedicated (in minutes) - Exam booking and payment	2.0 (2.5)	3.6 (4.2)	5.6 (5.8)	5.2 (4.5)	11.2 (8.8)	18.2 (17.3)
	Time dedicated (in minutes) - Exam reporting	1.5 (3.2)	2.1 (4.2)	2.3 (4.8)	2.5 (4.9)	4.5 (6.9)	6.0 (9.1)

Note. n.a.: not applicable.

Supplementary Table 3 - Gross wage of professionals

	Gross wage (2019)	Gross wage (2021)	Wage per minute (2021)
Clinician	€ 81,745	€ 84,197	€ 0.878
Nurse	€ 33,973	€ 34,992	€ 0.365
Radiology technician	€ 33,621	€ 34,630	€ 0.361
Resident	€ 25,500	€ 26,265	€ 0.274
Other healthcare personnel	€ 27,259	€ 28,077	€ 0.293
Administrative staff	€ 28,445	€ 29,298	€ 0.305

Notes:

- *On the basis of the information provided in the CCNL, we considered 5 working days per week, with a working time of 7 hours and 12 minutes per day (i.e., 432 minutes per day). In 2021, considering all the holidays and days of annual leave, we estimated a total of 222 working days. Overall, this translates into 95,904 working minutes, corresponding to approximately 1,598 working hours. Using these data, we computed the wage per minute of each professional.*
- *In estimating the wages of all professionals except residents, we averaged the wage reported in Conto Annuale for IRCCS, policlinics and local health authorities. For residents, we averaged the two different wages established by law according to seniority (€25,000 for the first two years of specialization, €26,000 for the remaining years).*

Supplementary Table 4 - Unit cost of instrumental exams and laboratory tests

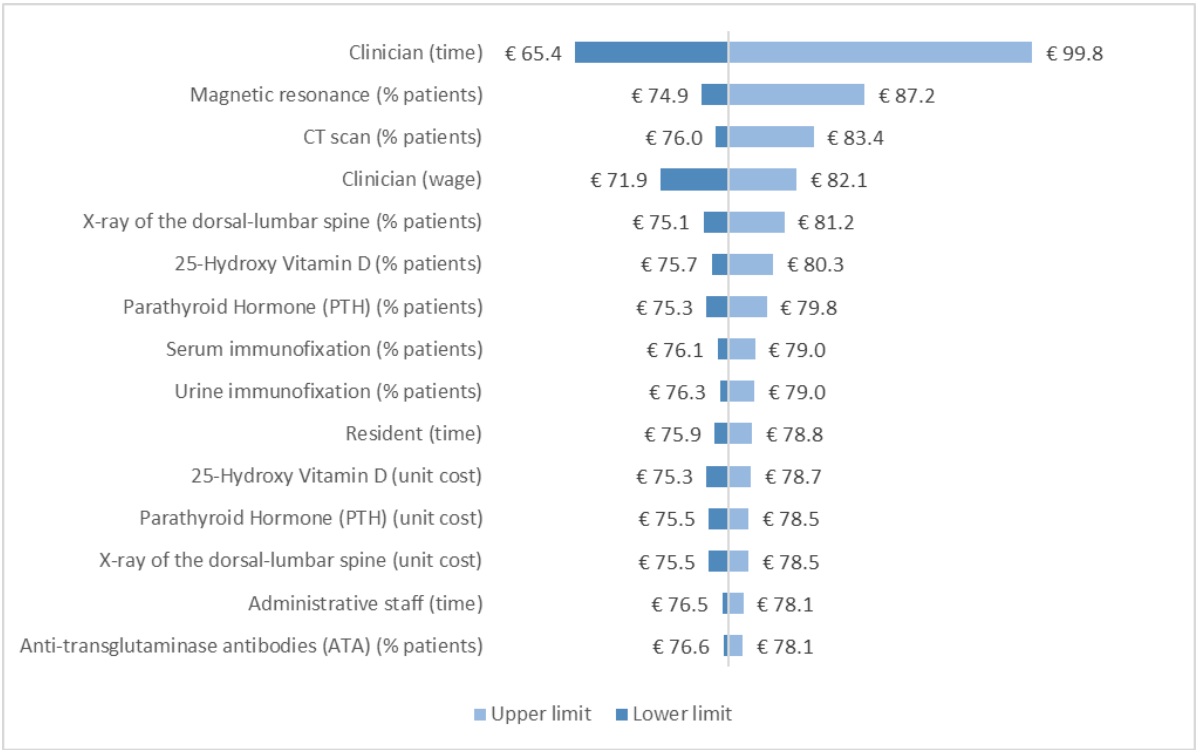
	Unit cost
Instrumental exams	
CT scan	€ 77.67
Magnetic resonance	€ 115.80
X-ray of the dorsal-lumbar spine	€ 34.60
Laboratory tests - I level	
24-hour urinary calcium	€ 1.13
Alkaline phosphatase (ALP)	€ 1.04
Calcemia	€ 1.13
Complete blood count	€ 3.17
Creatininemia	€ 1.13
Erythrocyte Sedimentation Rate (ESR)	€ 1.95
Phosphorus	€ 1.46
Protidemia (fraction)	€ 4.23
Laboratory tests - II level	
Ionized calcium	€ 1.13
Thyroid-stimulating hormone (TSH)	€ 5.46
Parathyroid Hormone (PTH)	€ 18.92
25-Hydroxy Vitamin D	€ 15.86
Overnight dexamethasone suppression test	€ 7.79
Serum immunofixation	€ 20.88
Urine immunofixation	€ 20.88
Anti-transglutaminase antibodies (ATA)	€ 9.98

Supplementary Table 5 - Total time dedicated to training (in minutes) by each healthcare professional

Professional figure	REMS mean (SD)			DXA mean (SD)			REMS - DXA mean (p-value)		
	Most conservative scenario (L)	Base-case scenario (M)	Least conservative scenario (H)	Most conservative scenario (L)	Base-case scenario (M)	Least conservative scenario (H)	Most conservative scenario (L)	Base-case scenario (M)	Least conservative scenario (H)
Clinician	158.1 (405.2)	307.3 (811.9)	1,105.4 (3,282.3)	592.0 (1,323.2)	848 (1,760.9)	1,081.0 (2,179.9)	-433.9 (n.s.)	-540.7 (n.s.)	24.4 (n.s)
Nurse	3.5 (9.0)	5 (13.2)	53.1 (133.1)	16.0 (26.3)	24 (42.0)	31.0 (59.0)	-12.5 (n.s.)	-19.0 (n.s.)	22.1 (n.s)
Radiology technician	9.2 (22.5)	31.5 (64.3)	46.2 (95.4)	747.0 (1361.5)	1,078 (1,866.2)	1,949 (2,642.4)	-737.8 (n.s.)	-1,046.5 (n.s.)	-1902.8 (0.016)
Resident	120 (415.0)	271.5 (824.0)	572.3 (1,652.6)	16.0 (38.6)	84 (152.8)	133.0 (234.3)	104.0 (n.s.)	187.5 (n.s.)	439.3 (n.s)
Other healthcare personnel	0.0 (0.0)	0.0 (0.0)	73.8 (266.3)	6.0 (19.0)	12 (37.9)	36.0 (113.8)	-6.0 (n.s.)	-12.0 (n.s.)	37.8 (n.s)
All professionals	**290.8 (815.9)**	**615.4 (1624.4)**	**1,850.8 (4,894.1)**	**1,377.0 (2643.9)**	**2,046.0 (3546.7)**	**3,230.0 (4,445.7)**	**-1,086.2 (n.s.)**	**-1,430.6 (n.s.)**	**-1,379.2 (n.s)**

Note. n.s.: not significant. Since the p-value is also affected by the sample size (the smaller the sample size, the higher the p-value), we should be careful in interpreting the lack of statistical significance of the difference in estimates (as it may be driven by the low number of observations)

Supplementary Fig. 1 - Sensitivity analysis – REMS



Supplementary Fig. 2 - Sensitivity analysis – DXA