As Long as the Quality is Assured

Honourable Rector Magnificus, distinguished audience,

In our time we tend to capture the notion of *quality* within definitions, measuring instruments, guidelines and protocols. Ideally, everything should be orderly, demonstrable and reproducible. This approach certainly has advantages: quality registries and evidence-based guidelines have clearly led to better outcomes and more uniform care across many domains.

At the same time, however, quality is not always so straightforward. What exactly do we mean by quality? How do we measure it? And how can we improve quality in a way that is truly appropriate to the context, the people, and the time in which we work? Moreover, is quality really the same for everyone, everywhere, at all times?

A sound quality standard today may, within only a few years, prove outdated. Furthermore, what constitutes good care for one patient may not be the same for another. Quality is therefore not solely a matter of measuring and box-ticking. It requires reflection, adaptation, and attentiveness to individual needs and changing circumstances.

I do not suggest by this that we should not strive for, or measure, quality—far from it. But I do wish to invite you to reflect anew, time and again, on what we regard as quality, and how we choose to define and apply it. Let us therefore explore a number of scenarios in which these questions come to the fore. Whether it concerns rare metabolic bone diseases, health care more broadly, education or research—the essence remains the same: what do we mean by quality, and how do we ensure that in seeking to define it we do not lose sight of its true meaning

Scenario 1

A 52-year-old postmenopausal woman is worried about developing osteoporosis. Both her mother and grandmother suffered multiple vertebral fractures before the age of sixty. She herself is otherwise healthy, though she has recently sustained an upper arm fracture following a simple fall in her kitchen. She eats healthily and exercises regularly. In accordance with the guideline, a bone mineral density (BMD) measurement is performed, together with a vertebral fracture assessment (a low-radiation spinal X-ray). This shows no vertebral fractures but reveals osteopenia. For those among us who are not internists or rheumatologists: osteopenia means bone density is below normal, but not low enough to meet the definition of osteoporosis. For the internists and rheumatologists: her T-score was –2.3. Consulting the guideline's flowchart, the recommended course is lifestyle advice, vitamin D supplementation, and possibly some calcium.

You explain to the patient that, according to our current quality standard, she does not need medication, and that she already follows the recommended lifestyle advice. You advise her to obtain vitamin D at the pharmacy, and no follow-up appointment is scheduled.

So far, so good—one might think.

Yet one year later, the patient returns via her GP with back pain. An X-ray now shows a vertebral fracture. The BMD measurement is repeated and remains unchanged, still within the osteopenic range. Once again you consult the flowchart, but this time the outcome is different. Based on the combination of the BMD values and the new grade 3 vertebral fracture, there is now even an indication for an osteoanabolic agent—the most expensive class of anti-osteoporotic drugs, which stimulate bone formation.

The patient asks why, if her values are the same, your treatment policy is now entirely different. You explain once again what you said a year earlier, adding that everything has changed because of the fracture. She then asks whether better-quality diagnostics should not have been performed a year ago, diagnostics that might have given a truer picture of her actual fracture risk.

Scenario 1 raises fundamental questions about quality, both in care and in diagnostics. In this case the guideline—the current quality standard—was followed. Yet one cannot help but wonder whether the patient herself would judge the quality of care in the same way. And perhaps, in hindsight, the clinician might also feel differently.

For most patients with a fracture, this approach is sound, particularly if other risk factors can be addressed. The real challenge lies in recognising those patients who may not benefit sufficiently from such an approach, and who may need something more. In this case the warning signs were present: a major bone fracture following a fall from standing height, low bone mass, a strong family history, and no other risk factors. In the absence of better diagnostics, a conversation about possible treatment—outlining the potential benefits and side-effects—might at least have been an option. The outcome may ultimately have been the same, since the medical approach was guideline-based, but one suspects that the patient would have experienced the care as being of higher quality had such a discussion taken place before the second fracture.

Improving care and diagnostics in bone diseases, including osteoporosis, is therefore an essential task for the future. Not only because this happens to be my field of interest, but also because of an ageing population and a persistent Western lifestyle. One in three women and one in five men will suffer an osteoporotic fracture. The ability to predict earlier and more accurately who is at risk is of great importance. Equally vital is knowing how best to start, adapt, or stop treatment, since osteoporosis is a chronic disease, and with increasing life expectancy we must think not only in terms of ten years but beyond.

At the LUMC we have worked intensively on this in recent years. Together with colleagues in Traumatology—Dr Termaat and Professor Schipper—and Orthopaedics, then Dr Van der Heiden, we developed the osteoporosis care pathway at the start of my tenure here. This pathway has since run continuously and been steadily refined. It marked the beginning of improving the quality of osteoporosis care at the LUMC and earned us the gold medal of the International Osteoporosis Foundation.

The care pathway also provided the foundation for a line of research into fracture risk assessment. My first PhD student, Frank Malgo—now a geriatrician—studied, among other things, the performance of vertebral fracture assessment (VFA), both in the literature and in our centre. His results prompted the manufacturer of the device to invest in higher-quality imaging, while colleagues in Nuclear Medicine, particularly Petra Dibbets-Schneider, made great strides in improving imaging and introducing novel techniques such as the Trabecular Bone Score (TBS).

The osteoporosis pathway also introduced the technique of Impact Microindentation, at that time unique in the Netherlands. This enabled us to measure an additional dimension of bone: its material properties. We found that patients with osteopenia and a fracture had equally poor bone material properties as patients with osteoporosis and a fracture. In other words, bone quality was equally poor, regardless of the BMD value.

We already knew that in certain conditions bone quality is impaired. Take acromegaly: patients suffer fractures despite bone density that does not fit with osteoporosis. We have now demonstrated that this is because the material properties of the bone are genuinely impaired. My PhD candidate, internist-endocrinologist Dr Manuela Schob from Switzerland, has shown that bone-strengthening medication—which we already know substantially reduces fracture risk—actually improves these material properties. This means the bone becomes truly stronger. In the future, this technique may therefore help us to identify patients like the woman in Scenario 1 more accurately.

We are also collaborating with Radiology and Nuclear Medicine to introduce an AI algorithm that detects vertebral fractures on routine CT scans performed for other reasons. The aim is to identify patients at highest risk more effectively. In BMD measurements we now routinely report a quality score of the spine—the Trabecular Bone Score—providing further insight into bone structure.

These collaborations have mainly focused on patients with fractures. In recent years we have also worked with Neurosurgery—Professors Peul and Vleggeert—to improve bone quality in patients without fractures, who are being prepared for spinal surgery. This applies to common spinal disorders such as degenerative disease, but also to rare bone conditions such as achondroplasia.

In addition, we work closely with partners outside the academic hospital, such as Dr Annegreet Vlug at the Jan van Goyen Clinic in Amsterdam. This collaboration is not only clinical but also scientific, and is crucial for the future, as data collection for highly prevalent diseases like osteoporosis will increasingly rely on partners outside the hospital setting.

If we return to the patient in Scenario 1, in 2025 she would likely undergo not only BMD and VFA, but also a TBS measurement. Given her concerns, she might also have a simple hardness test of the tibia (microindentation) performed in the outpatient clinic, providing insight into bone material properties. Together, these additional data might have altered the therapeutic decision. In future, AI-supported analysis of routine diagnostics may add further tools to assess bone quality and to translate these into clinical care.

Finally, it remains my wish, together with colleagues across the country, to establish a national osteoporosis registry. Such a registry would allow us to use larger and better-quality real-life data to optimise treatment plans for this highly prevalent chronic disease. Instead of simply reporting the number of BMD scans each year as a quality indicator, I hope that a national registry will offer more meaningful quality data—and that with process automation, we may move away from the manual counting that is still so often required for current quality indicators.

Scenario 2

A 12-year-old girl is seen by paediatric orthopaedics with a pathological fracture of the femur. She undergoes surgery, and the lesion proves to be cystic. Two weeks later, the pathology report arrives with the diagnosis of fibrous dysplasia. The parents are eager to know what this means for the future and what else they might expect.

The orthopaedic surgeon provides a general explanation of the condition and orders both blood tests and a skeletal scan. The girl is then invited to the combined clinic of the bone centre, where results are discussed immediately by both the endocrinologist and the orthopaedist. These scans reveal multiple sites of fibrous dysplasia—what we call polyostotic fibrous dysplasia. In addition, the blood results show a mild hyperthyroidism. On palpation, a distinct nodule is felt in the thyroid gland. Furthermore, phosphate—a mineral essential for bone—is found to be low. On further questioning, the girl reports fatigue and muscle complaints, which may well be related to her low phosphate.

A treatment plan for the hyperthyroidism is agreed. Given the palpable nodule and the known increased risk of thyroid cancer in these patients, a hemithyroidectomy is performed. She is also started on active vitamin D and phosphate supplementation, which normalises her phosphate levels. Because the scan shows craniofacial involvement with extension towards the orbit, an ophthalmology consultation is arranged. Parents and patient receive detailed counselling and are enrolled in a long-term care pathway coordinated between paediatric and adult endocrinology, which also includes systematic collection of clinical, quality-of-life, and pain data in the context of an observational study and European registry.

Twenty years ago, this girl would likely have been followed up only by orthopaedics. In the absence of other symptoms, she would probably not have undergone a whole-body scan, and her parents would have been given little information about the course of such a rare disease. But at the LUMC there has long been a special interest in metabolic bone diseases. Dr Neveen Hamdy invested years in building relatively large cohorts of patients with such rare conditions. Together with Professors van der Sande and Dijkstra from orthopaedics, a collaboration was established in 2014 that led to combined outpatient clinics, and in 2016 the first joint PhD candidate, surgical trainee Bas Majoor, was appointed.

This collaboration became the foundation not only of clinical care but also of education: fibrous dysplasia now features as a joint lecture in the undergraduate curriculum, delivered by orthopaedics and endocrinology together. Not because we expect students to memorise rare conditions, but because we want to demonstrate the value of collaboration—that good quality care does not depend on knowing everything yourself, but on recognising your own limitations and knowing when to involve colleagues.

The lessons learned from looking at patients and data together improved not only the quality of research but also the quality of care itself. Orthopaedic surgeons now routinely order blood tests and skeletal scans when suspecting metabolic bone disease, while endocrinologists will first conduct joint assessments and imaging before referring patients with musculoskeletal pain to orthopaedics. This has improved both the focus of consultations and the patients' expectations.

Building on the database, we discovered that women with fibrous dysplasia and McCune–Albright syndrome (FD/MAS) are at increased risk of breast cancer at a younger age. Our Dutch findings were confirmed using data from colleagues Michael Collins and Alison Boyce at the NIH. As a direct consequence, international guidelines will now recommend breast cancer screening in women with FD/MAS from the age of 40—a clear example of how research has translated into tangible improvements in patient care.

This was followed by the PhD thesis of Marlous Hagelstein-Rotman, who studied quality of life in patients with FD/MAS and examined the broad spectrum of disease manifestations, not only through our own database but also through the national pathology registry. We learned that this condition is highly variable and evolves over time. Several more theses are underway, including that of Maartje Meier, orthopaedic trainee, who has studied risk factors for fractures and deformities and extended the research into the laboratory through collaborations with Nathalie Bravenboer at Amsterdam UMC and Gabri van der Pluijm here in Leiden. Most importantly, she has shown that structured care pathways improve quality of life, even if patients continue to experience symptoms.

In recent years, additional collaborations have grown. A combined ophthalmology clinic was established with Stijn van der Meeren, orbit surgeon and PhD candidate, who studies ophthalmological outcomes in FD/MAS. Radiology and nuclear medicine have also become key partners: PhD candidate Wouter van der Brugge worked with Professors de Geus-Oei, Smit, and Vriens on imaging in FD/MAS. This led to the replacement of standard technetium bone scans by NaF-18 PET scanning at LUMC—another direct improvement to patient care.

Why am I listing all these names? Because I wish to emphasise how research, education, and clinical care can go hand in hand with quality improvement. Several PhD projects have already translated into international guidelines, changing clinical practice for patients. The FD/MAS story is, in my view, a wonderful example of how education, research, and care can reinforce each other and ultimately improve patients' quality of life—even in the absence of a definitive cure.

Of course, many questions remain. International collaboration will be essential. PhD candidate Oana Bulaicon from Romania has been central to initiating the DeFiD trial—a placebo-controlled study of denosumab in FD/MAS, designed to evaluate pain and quality of life. This project, launched with strong support from the patient association, illustrates the enormous regulatory and logistical hurdles faced by investigator-initiated trials. Without dedicated PhD candidates, such trials would simply not be possible.

Over the past years, care for rare bone and mineral disorders has grown significantly at LUMC through centralisation and through strengthening both internal and external collaborations. Work with oral and maxillofacial surgery, for example, has led to PhD projects on diffuse sclerosing osteitis of the jaw and medication-related osteonecrosis of the jaw, directly influencing international guidelines. Rheumatology trainee Ashna Ramautar is finalising her thesis on chronic non-bacterial osteitis, work that has laid the foundation for a national clinical trial on pamidronate. At the same time, we have participated in industry-sponsored studies in hypoparathyroidism, osteoporosis, and osteogenesis imperfecta, giving patients early access to novel therapies.

But setting up an investigator-initiated placebo-controlled trial, such as the DeFiD study or the PAPS trial, is becoming increasingly difficult. Regulatory requirements demand dozens of documents, frequent monitoring visits, and extensive reporting. Funding bodies rarely cover the full overheads. European registration requires repeating the process with yet more documentation. Multicentre participation adds further delays, as local interpretations of quality requirements differ. Without the perseverance of colleagues such as Professor van der Ven in Nijmegen, our DeFiD study would never have been extended to Radboud UMC.

Looking ahead, I am concerned that the growing regulatory burden, combined with limited research funding and clinical pressures, may mean that high-quality drug studies—especially for rare diseases—will become feasible only for the pharmaceutical industry. Investigator-initiated trials may disappear altogether unless we make the necessary investments in research infrastructure.

Scenario 3

After a day in the outpatient clinic – hopefully with the support of dictation, summarising, and executive assistance – you are finishing your consultations. You complete the last e-consults, take a final look at the home monitoring data on osteoporosis, and upload the data of patients with rare diseases into the European Register for Rare Endocrine and Bone Diseases (EuRREB).

Previous contributions to this register by you and your patients have already led to three patients being invited to participate in a phase 2 or 3 study of a new drug for their condition at another centre. Based on the information submitted by you and your patients, a research group in, for example, Germany has identified that this patient meets the inclusion criteria for a clinical trial with an existing drug that has come off patent. Just a few months earlier, within the European Reference Network, treatment protocols had been harmonised. This has enabled a European research consortium to include patients from across Europe within a short recruitment period. Instead of a trial requiring years to reach sufficient numbers, the target of 100 patients has been achieved within one year. Through video consultations, you are able to coordinate effectively between patient and researchers.

You end the day by providing digital supervision to one of the residents in training (AIOS), partly by joining a video consultation with a new patient to discuss the treatment plan you had drawn up together. The fact that you and your trainee are working from different locations does not hinder the progress of the consultation. The patient, meanwhile, has shared the link with a family member abroad, who is also able to join. You record the consultation, making the video available for 30 days for the patient's own use and for later discussion with the trainee.

But is this merely futuristic speculation? Will the quality of our teaching, healthcare, or research decline through such digitalisation? I believe not. If you look closely, much of this is already highly advanced. Since 2016, the European Reference Networks (ERNs) have been established with the explicit aim of improving care for rare diseases within the European Union. A key element of this has been the development of European Registers. In collaboration with Professor Faisal Ahmed, the European Register for Rare Bone and Mineral Disorders has merged with the register for Rare Endocrine Conditions, enabling us to combine datasets and patient information.

At present, the Registries team is in contact with 32 countries and 166 centres, with over 60,000 new patients registered who suffer from rare bone or hormonal conditions, and more than 4,500 patients for whom detailed datasets are available. Hundreds of patients are now also maintaining their own records within the register. With the invaluable help of paediatric endocrinologist and PhD candidate Ana Priego Zurita, the register has been built and further developed. Clinical data manager and endocrinologist Mariya Cherenko has mastered the intricacies of building and optimising modules, allowing us to be less dependent on third parties and retain more in our own hands.

Under the leadership of more than 15 international colleagues, disease-specific modules are now operational. I am particularly looking forward to the launch of the "Women's Health in Rare Endocrine and Bone Conditions" module and a large hypoparathyroidism module, in which we will collaborate with colleagues both in the Netherlands and abroad. The hypoparathyroidism module also offers an important opportunity for my newest colleague at the Bone Centre, Dr Femke van Haalen, to deepen her expertise in this disease and develop international collaborations. These collaborations are of crucial importance for the future, for progress is only possible through cooperation and connection: connection between patient and doctor, between physicians and researchers, and between centres. For example, together with colleagues across Europe, we have succeeded in collecting data on more than 600 patients with FD/MAS in just three years.

Thus, in the future, centralisation of care, collaboration in both healthcare and education, data collection, and technological developments will provide ample opportunities for research involving patients with rare diseases as well as more common conditions. This requires investment in infrastructure and technology, but above all in time, enthusiasm, and attention to one another. Take, for instance, the resident whose video consultation you supervised in this scenario. She worked from home that day, as roadworks had brought traffic to a standstill. The time saved by not travelling allowed her to read more about the subject, and you as supervisor needed to do little more than observe the interaction between trainee and patient. You even had the opportunity to document this in a Brief Clinical Assessment (Korte Klinische Beoordeling, KKB), concluding that the trainee had achieved her learning objectives for this stage. Together, you decided to progress her to EPA level 4, which marks the trainee as competent to function independently without supervision. The systematic discussion of learning goals, assessment methods, and structured feedback within the portfolio has significantly advanced the professionalisation of training in internal medicine, rheumatology, and other specialties. Where years ago some regarded our neutral rotation model for endocrinology trainees with scepticism, it is now integrated in most training programmes and subspecialties. The model of teamwork – in which the supervisor teaches the trainee but also learns from the trainee's fresh insights – is, I hope, now fully embedded across our training region in Leiden, supported by the Internal Medicine Training Centre led by Eveline de Lange and our network of dedicated trainers. Together, we ensure that tomorrow's doctors possess a broad foundation of knowledge, with depth where needed. The professional of the future will be increasingly digitally skilled and will collaborate with patients to collect data and knowledge in order to learn from and with each other. The most important prerequisite for quality in this respect is the willingness to address shortcomings, to learn from one another, and to remain open to change. If that happens, the quality of care, research, and education will be assured.

Returning to the questions posed at the beginning of this oration:

1. What is quality? Quality is a term we use to quantify something that is not easily quantified. As such, it is something that is subject to change.

2. How do you measure quality? This varies. It is important to discuss in advance which measurement you will perform and when, taking into account that insights may change over time.

3. How do you improve quality? By critically evaluating and taking action with a clear plan. This may involve a medication plan, for example to improve bone quality, providing feedback through a KKB within the training programme, improving the recording of research data, or even introducing a PDCA cycle. In all cases, it is essential to formulate a goal, choose a method, and include interim checks and evaluation points.

I have mentioned many collaborative partnerships in this lecture. For me, these form the foundation of this professorship; without these colleagues, I would not have been able to establish the research and care pathways mentioned. I realise that this list is by no means complete and I hope that no offence is taken.

I would like to take this opportunity to thank a number of people in particular, who have made this professorship possible or have had a significant impact on my development: First, the members of the Executive Board of Leiden University, the Board of Directors of the LUMC, and the divisional board of Division 2, for the trust placed in me to take up this professorship again after 12 years.

Professor Rabelink, dear Ton, thank you for the trust in me as a trainer in Internal Medicine and bone specialist. Without your vision, there would have been no Bone Centre following Socrates' retirement, and the role of trainer also seems to suit me well.

Professor Pereira, my supervisor and former section head, and Professor Dekkers, current section head of Endocrinology, thank you for your dedication and trust. Alberto, I am especially grateful for the excellent introduction to the world of ERNs and the successful matching with Faisal. Faisal, although we have mostly collaborated remotely over the past five years, I have greatly enjoyed it. I look forward to future projects, as the EuRREB project is gradually entrusted more and more to the Leiden team.

Professor Papapoulos, dear Socrates, during the eight months in which you supervised my endocrinology clinic, you planted a seed that has since grown successfully. Thank you for the introduction to the field and for our lively discussions.

Neveen, esteemed Dr Hamdy, thank you for the enjoyable conversations, whether over a light lunch or otherwise, and for teaching me the finer points of patient care for rare diseases. Without you, the CNO and Fibrous Dysplasia data collections would never have come about.

To all my other colleagues within the Endocrinology staff and the training team, and certainly beyond, thank you for your collaboration and support.

In particular, I would like to acknowledge the medical assistants and nurse specialists of the Bone Centre: Lida, Wilma, and Joyce. Without you, the outpatient clinic would not run smoothly and patient inclusion in studies would not have been possible. The Osteoporosis Care Pathway would not have been as successful without the contributions of nurse specialists Yvonne Bernards and the now former Petra Beckers.

Finally, my dear parents and family: without you, I would not be here, literally and figuratively, to borrow the words of the children. This professorship is a family endeavour. You now understand well what osteoporosis and bone diseases entail, and why I am so committed to this field. Thank you for your love and patience when I am attending meetings at impossible hours or at conferences. I will not promise that things will be quieter from now on; you know me.