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Standardization and Pretrial Quality Control

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4.1. Introduction

Before initiating a clinical trial, the sponsor must be assured that the equipment and techniques used can adequately answer the research question. In multicentre trials, each centre might have instruments from different manufacturers, compounding the issues involved in initiating the trial. The investigator must be assured of the following:

1. The instruments and anatomical site chosen are adequate to classify the osteoporotic status of subjects on entry to the trial and monitor the anticipated change in bone mineral density (BMD) or quantitative ultrasound (QUS)
2. Staff are adequately trained on the equipment to be used
3. Long-term precision is known within the subject group studied
4. Differences between instruments are known and, as necessary, a crosscalibration is derived
5. Subjects radiation doses are known.

The aim of this chapter is to summarize the equipment tests required before establishing a clinical trial to reassure the investigator that each centre is adequately prepared to begin clinical work. It will cover the following points:

1. Differences between dual energy X-ray absorptiometry (DXA) instruments or ultrasonometers
2. The choice of phantom for crosscalibration
3. The review of daily quality control (QC) before the trial commences
4. Accuracy
5. Precision: both long-term and short-term precision, \textit{in vitro} and \textit{in vivo}
6. Crosscalibration and standardized BMD
7. The radiation dose.

The chapter will also consider the preparations for using X-ray morphometry (either radiographic or DXA morphometry). Only Lunar (GE Healthcare,
Madison WI, USA) and Hologic (Bedford MA, USA) densitometers will be considered because this covers 95% of the world market.

4.2. Equipment Differences: DXA

The calibration differences in BMD measured on different manufacturers’ DXA equipment are known and documented\(^1\)–\(^4\), in addition to the intramanufacturer instrument differences.\(^5\)–\(^8\) The Lunar densitometers are calibrated against an ashed bone standard\(^9\) and give measured results some 10–15% higher than those obtained for the same subject measured with either Hologic or Norland (Cooper Surgical, Trumbull, CT, USA) instruments, which are calibrated against a hydroxapatite standard.\(^10\) Figure 4.1 demonstrates the calibration difference between Lunar and Hologic devices in vivo on a Bland and Altman plot. The difference in BMD measured on the two instruments is plotted against the mean BMD, to demonstrate any systematic differences between the instruments. The mean difference between the two systems was measured as 0.12 g/cm\(^2\). This implies that, when establishing a multicentre clinical trial, investigators tend to choose centres with equipment from the same manufacturer. However, if studies exceed 10 to 12 instruments this is not necessary because crosscalibrations can be obtained that are adequate to compare groups of subjects at baseline and demonstrate a treatment effect within the subject group. It should be noted, however, that

\[ \text{FIGURE 4.1.} \quad \text{Bland and Altman plot of Lunar DPX-L and Hologic QDR 2000 lumbar spine BMD in vivo. The mean difference is 0.12 g/cm}^2. \text{ There is a significant regression of the difference in BMD on the mean BMD} \ (r = 0.46; P < 0.0001). \]