Clinical Investigation Plan (CIP)

Study Title:	IBEX Trueview® Study
Protocol Number:	IBX/SP1701
Author(s):	Kurt Scott
Sponsor:	IBEX Innovations Ltd.
Chief Investigator:	Professor Amar Rangan
Version:	1.7
Date:	24th September 2019

CIP Approvals

Chief Investigator

I agree to conduct this study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by myself, the sponsor, Health Research Authority (HRA) and Ethics Committee.

AMAR RANGAN		30 OCT 2019
Chief Investigator	Signature	Date

Principal Investigator

I agree to conduct this study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the CI, sponsor, Health Research Authority (HRA) and Ethics Committee. I agree to await Ethics Committee approval of the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrolment in the study, to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

AMAR RANGAN		30 OCT 2019
Principal Investigator	Signature	Date

Confidentiality Statement

This document contains confidential information belonging to IBEX innovations ltd. and South Tees Hospitals NHS Trust except as may be otherwise agreed to in writing by both parties, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

Sponsor

The present study has been reviewed and approved.

NEIL LOXLEY	N. Loxley	27/09/19
Sponsor Representative	Signature	Date

Contents

1. Amendment History

CIP Version No.	Date Issued	Author(s) of Changes	Details of Changes
1.0	05/11/18	K. Scott	First version issued
1.1	12/12/18	K. Scott	Switched order of phases to match objectives and be consistent with other documentation.
1.2	09/01/19	K. Scott	• Clarified primary objective and primary endpoints. See amendments in sections 3 and 5 • Clarified safety endpoints. See sections 3 and 5 • Added clarification about blinding to section 6.3 • Added clarification to replacement of withdrawn subjects in section 8.4.1 • Added explanation of safety analysis and analysis populations in section 11
1.3	16/01/19	K. Scott	• Added clarification to analysis of data from withdrawn patient to avoid bias in section 11.1.2 • Revised section 11.5 to describe handling of missing data • Added clarification of statistical analysis methods, including description of confidence intervals, in section 11.1
1.4	18/01/19	K. Scott	• Added clarification to safety analyses for each endpoint in section 11.1.3 • Removed any claims about dose reduction potential of the technology
1.5	25/01/19	K. Scott	• Added definition of hypotheses in section 5.3 • Amended procedure for handling missing data in section 11.5
1.6	14/03/19	K. Scott	• Added requirement to collect daily calibration images in Phase 1 to monitor DR system drift (section 6.3.1)
1.7	24/09/19	K. Scott	• Updated references to Trueview software version (from 1.0 to 1.1.0)

2. Abbreviations

ADE	-	Adverse Device Effect
AE	-	Adverse Event
ASG	-	Anti-scatter Grid
BMD	-	Bone Mineral Density
CRF	-	Case Report Form
CI	-	Chief Investigator
CIP	-	Clinical Investigation Plan
CSR	-	Clinical Study Report
CRO	-	Contract Research Organisation
DMC	-	Data Monitoring Committee
DR	-	Digital Radiography
DEXA	-	Dual Energy X-ray Absorptiometry
EDC	-	Electronic Data Capture
GDPR	-	General Data Protection Regulation
GP	-	General Practitioner
GCP	-	Good Clinical Practice
HRA	-	Health Research Authority
IFU	-	Instructions for Use
ICMJE	-	International Committee of Medical Journal Editors
JCUH	-	James Cook University Hospital
MHRA	-	Medicines and Healthcare products Regulatory Agency
MCAR	-	Missing Completely at Random
NHS	-	National Health Service
NIM	-	Non-inferiority Margin
OEM	-	Original Equipment Manufacturer
PC	-	Personal Computer
PI	-	Principal Investigator
R & I	-	Research and Innovation
REC	-	Research Ethics Committee
SADE	-	Serious Adverse Device Effect
SAE	-	Serious Adverse Event
SME	-	Small to Medium Enterprise
SAP	-	Statistical Analysis Plan
SOC	-	System Organ Class
USADE	-	Unanticipated Adverse Device Effect

3. Clinical Investigation Synopsis

Clinical Investigation Title	IBEX Trueview® Study
Sponsor Reference Number	IBX/SP1701
Clinical investigation Design	Single-centre, non-randomised, prospective, crossover study. Each patient will act as own control. Parallel recruitment between 2 phases.
Clinical investigation Participants	Patients who meet the following criteria will be considered eligible for Phase 1 of study: 1. Caucasian male or female, at least 50 years of age Attending for a DEXA scan of Neck of Femur (for measurement of bone mineral density); 2. Patient able to comprehend and sign the Informed Consent prior to enrolment in the study Patients who meet the following criteria will NOT be eligible for Phase 1 of the study: 1. Women who are pregnant or are breastfeeding 2. Concurrent participation in another experimental intervention or drug study 3. Has an implant or other radio-opaque foreign body in the location of the assessment 4. Unwilling or unable to provide informed consent Patients who meet the following criteria will be considered eligible for Phase 2 of study: 1. Male or female, 18 years of age or over, attending orthopaedic outpatient's clinic and requiring plain radiographs of wrist or shoulder or pelvis; 2. Patient able to comprehend and sign the Informed Consent prior to enrolment in the study Patients who meet the following criteria will NOT be eligible for Phase 2 of the study: 1. Women who are pregnant or are breastfeeding 2. Concurrent participation in another experimental intervention or drug study 3. Unwilling or unable to provide informed consent 4. Currently wearing a cast on assessment site that is not intended to be removed prior to radiographic assessment 5. Has an implant or other radio-opaque foreign body in the location of the assessment
Number of Participants	Phase 1 – 130 Phase 2 – 60
Follow-up Duration	No follow-up Patient participation in the study ends once the radiographic images are obtained.

Planned Clinical investigation Period	Phase 1 – 5 months Phase 2 – 5 months
Primary Objective	To demonstrate the effectiveness of the Trueview software in obtaining bone mineral density data at an accuracy equivalent to that of a DEXA on a standard DR system without negatively impacting the diagnostic image quality of the radiograph
Safety Objective	Confirmation of the safety of using Trueview Software
Primary Endpoints	Bone mineral density as determined from the Trueview software and DEXA system. (Phase 1) An image scoring assessment by 2 independent radiologists will determine the image quality of images collected on both the standard system and using the Trueview software. The scores will be compared to determine the Trueview image quality compared to the standard images. (Phase 2)
Safety Endpoint	The safety endpoint will be the nature and frequency of all adverse events observed during the clinical investigation including their timing, severity and relatedness to the investigational device and/or clinical investigation procedures.
Device Name	IBEX Trueview
Manufacturer Name	IBEX Innovations Limited
Principle Intended Use	Gridless scatter removal in digital radiography examinations
Length of Time the Device has been Used	The Trueview software has not previously been used in clinical practice.

4. Introduction

4.1. Clinical Investigation Details

4.1.1. Clinical Queries

Clinical queries should be directed to Factory-CRO who will direct the query to the appropriate person. Details can be found in Appendix B.

4.1.2. Sponsor

IBEX Innovations Limited is the main research sponsor for this clinical investigation. For further information contact Kurt Scott at:

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4.1.3. Funder

This study is being funded as part of a Horizon 2020 project entirely funded by the European Commission under project number 777835. IBEX is the sole beneficiary of the grant and will administer the funding of this study.

4.1.4. Document Summary

This CIP describes the IBEX Trueview® clinical investigation and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the clinical investigation. Problems relating to this clinical investigation should be referred, in the first instance, to the Sponsor Representative.

This clinical investigation will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the CIP, the GDPR, ISO 14155:2011 and other regulatory requirements as appropriate.

4.2. Device Summary and Purpose

The results of non-clinical studies show that IBEX Trueview software serves two primary purposes. Firstly, the algorithms used to determine the scatter profile of the sample can also return a measurement of the bone mineral density (BMD) of the sample without the need for a separate dual energy X-ray absorptiometry (DEXA) scan.

Secondly, it can digitally remove the effect of scattered X-rays from an image without the need for an anti-scatter grid (ASG), resulting in images of equivalent or better quality than typical digital radiographs taken with an ASG.

4.3. Manufacturer Details

The software is developed and supplied by IBEX Innovations Ltd. IBEX was founded by Dr Gary Gibson in 2010 and took off in 2011, after investment to develop and commercialise an innovative X-ray detector technology capable of generating high sensitivity materials information from standard X-ray detectors. In June 2018, IBEX was awarded ISO9001:2015 and ISO13485:2016 accreditation by auditors Lloyds Register Quality Assurance.

The IBEX technology has developed rapidly from an initial concept to fully engineered solutions, and the company is now seeing increasing commercial adoption in security, food inspection and medical markets.

IBEX employs a team of highly-skilled and dedicated scientists, engineers and business professionals at its modern facilities on NETPark, Sedgefield and the development of the technology is supported by venture-capital funding from Northstar Ventures, IP Group and Nordson Incorporated.

4.4. Investigational Device Information

Version 1.1.0 of the Trueview software will be used during this study. For the purposes of the investigation the software will be installed on a standalone PC provided by IBEX. IBEX will perform an installation verification prior to delivery of the PC to ensure the correct software version is being used. Details of the software version will be available in the software through an “About” screen in the menu options.

The software has been developed following recognised ISO standards. These standards ensure design and change traceability for the software.

Since the device is software based, it will not come into direct contact with any tissues or body fluids.

The software is designed to be integrated into an OEM system as a library of functional code but in order to test it in an "offline" mode it will be driven by a fully tested general user interface which is not considered to be part of the device.

4.5. Intended Use

A typical fracture assessment using a digital radiography (DR) system requires the patient to stand, sit or lie in a predetermined position to allow the radiographer to take an X-ray image of the affected body part. Typically, DR systems are fitted with an automatic exposure control which regulates the X-ray exposure time to ensure that a usable image is captured whilst minimising patient dose. For body parts that are prone to scatter X-rays, and ASG is normally used to limit the image damaging effect of such scattered X-rays.

This device is intended to be used during all routine radiographic examinations of fractures and will replace the requirement to use an ASG in situations where one is currently required. It will also provide an instant indication of bone health to clinicians which can inform further treatment pathways.

4.6. Required Device Training

The Trueview software will be installed on a separate computer to be used alongside the standard radiography system set-up. Radiographers will be trained in the operation of the software which will include loading and processing images for scatter correction and also loading images and selecting regions of interest for the bone mineral density calculations. Training will also be given on the calibration procedure. Full instructions are provided in the Instructions for Use document.

IBEX will be responsible for providing adequate training to all investigation staff and will keep accurate records of who was trained and the date of the training. It is the responsibility of the CRO to ensure that all members of the investigation team are invited for device training.

4.7. Justification of Study Design

4.7.1. Standards of Care

4.7.1.1. General Radiography

Radiography is a medical imaging process that relies on the use of X-rays to visualise the internal structures of the human body. The resulting greyscale images are formed by the X-rays passing through the subject to a digital X-ray detector. Contrast in the image is generated by the varying levels of X-ray absorption by the different tissues in the subject (i.e. bone absorbs more X-rays than soft tissue).

Digital radiographs are commonly used by orthopaedic clinicians to diagnose and assess fractures and other bone or joint health related conditions. Following a referral for a radiography to be conducted, a patient will attend the radiology department. The radiographers will position the patient either on the couch or against the wall mounted detector and capture an X-ray image of the desired body part using automatic exposure control settings on the radiography system.

Generally, the patient will receive a series of images consisting of various projections that enable the viewing clinician to make an accurate assessment and diagnosis. For the body parts to be imaged in this study, the recommended series (Whitley, et al., 2015) consist of the following images:

Wrist: Posteroanterior (PA) and lateral views

Shoulder: Anteroposterior and lateral views

Pelvis: Anteroposterior view

Radiographers will briefly assess images as they are taken and, in the event that an image is deemed unusable (due to under or overexposure or poor positioning for example), they will take a second exposure to ensure that the radiologists have the information they require for diagnosis. For the purposes of this study, any patient requiring repeat exposures as part of the standard assessments will be withdrawn from the study.

4.7.1.2. DEXA

Dual-energy X-ray absorptiometry is a technique used to aid in the diagnosis of osteopenia and osteoporosis. A DEXA system usually consists of either a dual energy (switching kVp) fan-beam X-ray source with a linear detector or a single energy source with a linear sandwich detector (two detectors to detect different energy levels).

A patient would generally be referred either by their GP or a fracture liaison service for their first DEXA scan, with follow-up scans every 3 years. At the clinic, they are carefully positioned on the DEXA couch and the system horizontally scans across the assessment region.

Generally, lumbar spine or neck-of-femur regions are scanned to calculate bone mineral density values which are then used to provide an indication of the patient's bone health. If cases where implants, fractures or other artefacts may be present in these regions, the forearm can also be used (Lorente-Ramos, et al., 2011).

4.7.2. Current Reference Standard

4.7.2.1. Digital Radiography

Digital radiography is a standard imaging tool for most modern hospitals and has replaced film based computed radiography in most of the market in the developed world.

Despite its prevalence, advancements in the technology have been limited in recent years, with manufacturers relying on incremental improvements in detector capabilities or on software post-processing to differentiate their products.

A key issue affecting all digital radiography systems is that of scattered X-rays, which can degrade images to the point of being unusable if no provision is made to deal with them. While some manufacturers are releasing software-based approaches to coping with X-ray scatter, they are mostly only applicable to very specific body-parts or indications and are not applicable in the general case. As such, physical anti-scatter grids are still the most commonly used method of dealing with X-ray scatter.

For the purposes of this study, a Siemens Ysio DR system will be used as the reference standard for comparison. Whilst it is not one of the newest models available, it is considered to have all of the required features and performance capabilities required of a typical digital radiography system.

4.7.2.2. DEXA

Osteoporosis is a condition that affects the bones in which a loss of bone mass can result in fragility leading to an increased risk of fractures. Currently, the most widely accepted method of obtaining a useful indicator of bone health is to measure bone mineral density using a DEXA system (Institute of Bone Health, 2017).

The DEXA market is dominated primarily by GE Medical and Hologic, who produce a variety of systems under the Lunar and Discovery lines respectively. The primary functionality of these systems is to conduct a scan of the lumbar spine of neck of femur to calculate the bone mineral density of a patient. Most modern systems also offer the ability to conduct fat vs lean tissue compositions and other compositional measurements of the body.

A key thing to note about this key functionality is that whilst they perform the same function in calculating BMD, the actual results vary significantly from manufacturer to manufacture due to the use of propriety algorithms and calibration routines. In one study that measured the European Spine Phantom on a number of systems from different manufacturers, GE Lunar systems were found to

overestimate BMD by as much as 22% on average while for the same region the Hologic systems overestimated by 6% (Park, et al., 2015). This demonstrates that the self-consistent precision of a given DEXA system is more important than its accuracy with relation to a known ground truth BMD.

BMD measured on a DEXA system is fed into the FRAX® system (University of Sheffield, 2018), along with other clinical factors, to provide a ten-year probability of fracture for the patient. Crucially, the calculation tool requires a knowledge of the DEXA system used in order to properly account for the discord between manufacturers algorithms.

For this study, A GE Lunar system will be used as the gold standard comparator, while the Trueview BMD will be calculated from images collected on a Siemens Ysio DR system.

4.7.3. Cadaver and Phantom Results

The Trueview software has been tested to show that it can reliably produce both scatter corrected images of acceptable diagnostic quality and BMD information to the same level of accuracy as a DEXA system. A variety of tests were conducted to demonstrate these capabilities are described below. Detailed discussion of these results is available in the Summary of Pre-Clinical Testing document.

4.7.3.1. Scatter corrected image quality

Firstly, a qualitative assessment of the image outputs was conducted. Images collected using a standard system were compared with images processed using the Trueview software at the same detector dose. The images have been assessed by competent clinicians and the opinion is that Trueview images are of acceptable diagnostic quality.

Secondly, a quantitative assessment was conducted using accepted methodology. Images of the internationally recognised “CDRAD” contrast and detail phantom (Al-Murshedi, et al., 2018) were collected on both a standard system and the Trueview software and the processed images assessed by the included software to quantify performance. Images were taken on the standard system both with and without an ASG present to highlight the negative effect of scatter on the image.

The CDRAD software outputs a measure of the fine detail and contrast visible in the resulting images and the comparison shown in Figure 4.1 below demonstrates that the Trueview software is as effective as an anti-scatter grid at 33% lower dose.

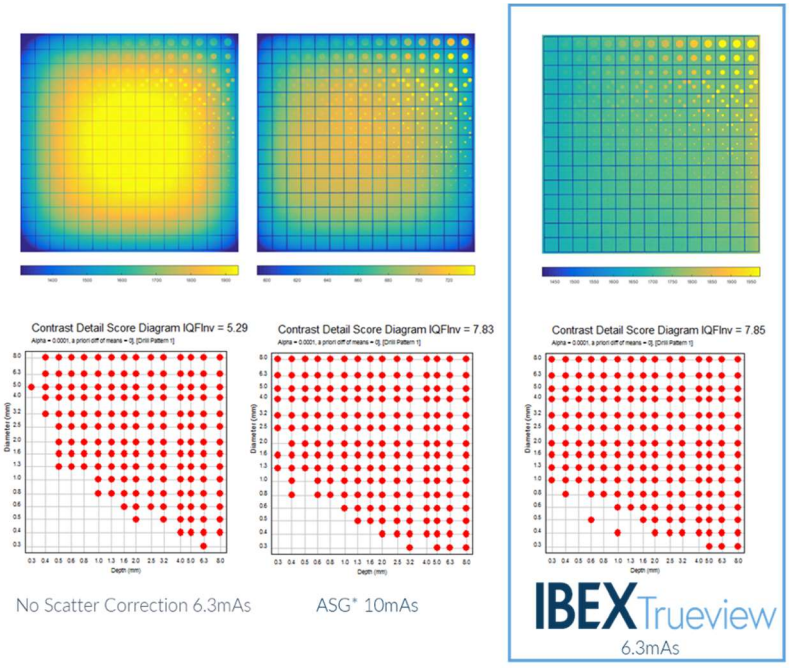

Figure 4.1 - Comparison of CDRAD performance between Standard system without ASG (left) and with ASG (centre) and Trueview software (right)

4.7.3.2. BMD Accuracy and precision

The BMD accuracy of the Trueview software was compared to DEXA by collecting images of a medical phantom, with a known ground truth, on both a GE Lunar DEXA system and a DR system equipped with the Trueview software. Following processing it was demonstrated that the Trueview software produce results that were within the same level of accuracy as the GE Lunar DEXA system as shown in Figure 4.2 below.

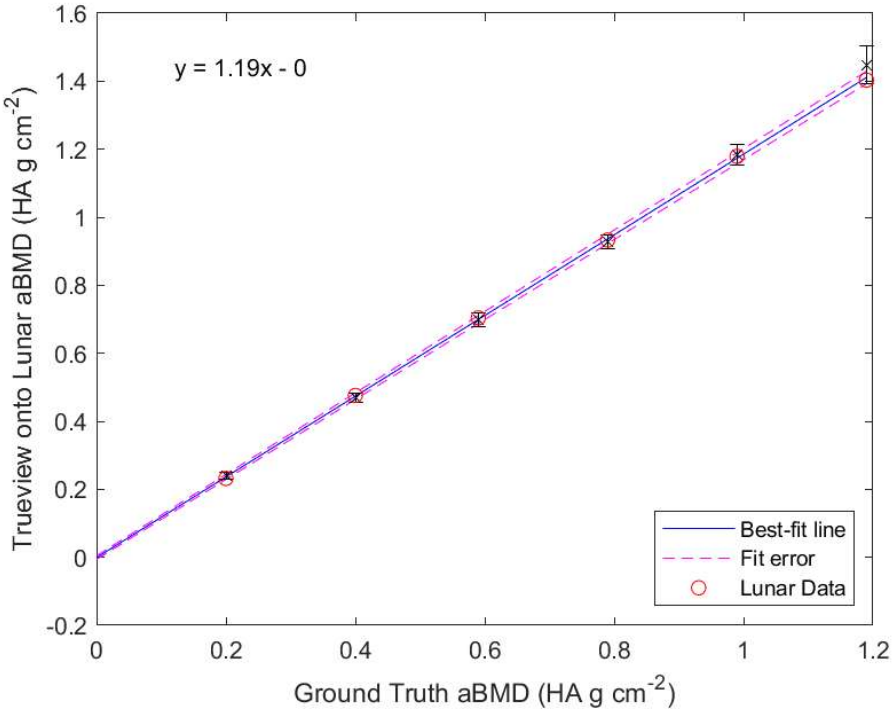

Figure 4.2 - Comparison of Trueview BMD to GE Lunar DEXA BMD

4.7.4. Benefits and Risks

The Trueview software has the potential to significantly improve the diagnostic capabilities of standard DR systems. This study has been designed to demonstrate that the software can provide equivalent image quality without the need for an anti-scatter grid and also that the software is capable of providing additional diagnostic information from a single scan in the form of a bone mineral density measurement.

The potential benefits to future patients and the NHS from such information are:

- Population wide bone health information (by virtue of being able to assess bone health on every patient receiving a digital radiograph rather than limited to those referred for DEXA)
- Earlier diagnosis of osteoporosis and other bone health conditions
- Improved image quality for radiographic assessments
- Lower equipment cost for a single DR system equipped with Trueview software than a separate DR system and DEXA system

There are some risks that could prevent some of these benefits from being achieved that are mainly technical. In all cases, these risks have been mitigated as far as possible through technical development and testing. The potential risks are:

- Image quality with Trueview is not acceptable
- BMD accuracy is not as good/consistent as DEXA
- Software doesn't not work as expected in all recommended use cases

The product risks are discussed in detail in the Risk Analysis document.

In addition, there is also a small health risk to patients involved in the study as they may be subject to additional radiographic scans (see section 6.3) that they wouldn't normally have received, thus increasing the radiation exposure to those patients. The exclusion criteria for recruitment will limit the negative effects of this exposure by excluding children and pregnant women from the study and also by focussing on body parts that are less sensitive to the effects of ionising radiation.

4.7.5. Radiation Risk Assessment

An assessment of the risk posed by the use of ionising radiation has been conducted by a lead clinical radiation expert and a lead medical physics expert. The total amount of radiation potentially received by a patient in this study ranges from 0.2-0.6 mSv, depending on trial arm. This is equivalent to a few months of average natural background radiation in the UK.

Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study is 0.004 %, which is very low. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

The risks imposed by the additional exposures are considered to be minimal in comparison to the potential benefits offered.

4.7.6. Justification Statement

We believe that the potential benefits that the Trueview software could offer are significant and could enable more efficient use of digital radiography systems by eliminating the need to use an ASG. Additionally, by enabling clinicians to obtain an indication of bone health at the time of fracture diagnosis using a digital radiography system, it could offer significant benefits in the reduction of fragility fractures and their associated health and social care costs.

The study has been designed in a way to limit the additional radiation exposure to patients as much as possible. The additional exposures have been deemed acceptable by both a lead Clinical Radiation Expert and a lead Medical Physics Expert.

5. Clinical Investigation Objectives

5.1. Objectives

5.1.1. Primary Objective

To demonstrate the effectiveness of the Trueview software in obtaining bone mineral density data at an accuracy equivalent to that of a DEXA on a standard DR system without negatively impacting the diagnostic image quality of the radiograph

5.1.2. Safety objective

Confirmation of the safety of using Trueview Software

5.2. Endpoints

5.2.1. Primary endpoints

The following parameter will be used to assessed BMD for each image:

- Bone mineral density (BMD) as determined from the Trueview 1.1.0 software and DEXA system.

The following parameter will be measured to indicate the image quality:

- An ordinal categorical scoring scale of [1 2 3 4 5], wherein the low-point score (1) indicates the worst quality, the mid-point score (3) indicates adequate quality a high-point score (5) indicates exceptional quality. Each image will be assessed by 2 radiologists.

5.2.2. Safety endpoint

The safety endpoint will be the nature and frequency of all adverse events observed during the clinical investigation including their timing, severity and relatedness to the investigational device and/or clinical investigation procedures.

5.3. Hypotheses

In order to demonstrate the primary objective, the study requires two distinct phases involving mutually exclusive patients being assessed using two separate reference machines for two different indications. The primary hypothesis being tested in each phase is given below.

5.3.1. Primary Hypothesis (Phase 1)

One of the main purposes of the Trueview software is to determine the BMD of samples without the need for a separate DEXA scan. The first phase of the study has been powered to demonstrate that there will be equivalence between the Trueview and the DEXA. It is expected that the paired difference between the Trueview and the DEXA will be within 0.08 (refer to Section 12.2.2 for the sample size considerations and determination of equivalence). With 130 completed subjects in phase 1, the study will have 90% power to demonstrate that the Trueview outcomes are equivalent to the reference standard, with a p-value of 1%.

5.3.1.1. Phase 1 hypothesis definitions

Null Hypothesis: The average differences between Trueview and DEXA BMD are not confined within 0.08.

$$H_0: \mu_D < -0.08 \; or \; \mu_D > 0.08$$

$$where: \mu_D = \mu_{Trueview-}$$

Alternative Hypothesis: The average differences between Trueview and DEX BMD are confined with 0.08

$$H_1: -0.08 < \mu_D < 0.08$$

$$where: \mu_D = \mu_{Trueview-DE}$$

If the p-value is less than or equal to 0.01, then the null hypothesis will be rejected in favour of the alternative, that Trueview and DEXA average BMD accuracy are equivalent.

5.3.2. Primary Hypothesis (Phase 2)

One of other main purposes of the Trueview is to digitally remove the effect of scattered X-rays from an image without the need for an ASG, resulting in images of equivalent or better quality than typical digital radiographs taken with an ASG. The second phase of the study has been powered to detect non-inferiority of the image quality between Trueview and standard radiography. It is expected that Trueview will provide an image quality within 10% of the standard radiography (refer to Section 12.2.1 for the sample size considerations and determination of the non-inferiority margin). With 60 completed subjects in phase 2, the study will have 90% power to demonstrate that the image quality by Trueview is non-inferior to that of standard radiography, with a p-value of 1%.

5.3.2.1. Phase 2 hypothesis definitions

Paired Means T-test to determine if Trueview has non-inferior average image quality compared to standard radiography.

Null Hypothesis: The average differences between Trueview and standard radiography image quality scores are less than or equal to -0.3.

$$H_0: \mu_D \leq -0.3$$

$$where: \mu_D = \mu_{TrueView-Standa}$$

Alternative Hypothesis: The average differences between Trueview and standard radiography image quality scores are greater than -0.3.

$$H_1: \mu_D > -0.3$$

$$where: \mu_D = \mu_{TrueView-Standard}$$

If the p-value is less than or equal to 0.01, then the null hypothesis will be rejected in favour of the alternative, that Trueview has non-inferior average image quality compared to standard radiography.

6. Clinical Investigation Design

6.1. Study description

The clinical investigation of the Trueview software comprises of two phases. The reason for splitting the study into two phases is that the indications and populations will differ in order to collect the required data to demonstrate the primary objective.

Phase 1 will compare the accuracy of the BMD data calculated by the Trueview software with that obtained from the gold standard DEXA system.

Phase 2 will serve to demonstrate that the Trueview software can accurately predict and remove the effect of scattered X-rays without the need for an ASG in order to produce diagnostic images of equivalent or better quality than the standard digital radiography system setup.

Both phases will be conducted as non-randomised, prospective, crossover studies in which each patient will act as their own control. Recruitment of patients for both phases will occur in parallel.

In both phases, patients will be screened as defined in section 11. Eligible patients will be provided study information prior to their visit and will be asked if they wish to participate when they attend the fracture or DEXA clinics as outpatients. Once patients have consented, they remain in the study only until they have had their assessments. They will exit the study upon the completion of their outpatient radiographic assessment. There is no follow-up with patients as the Trueview software outputs will not be used to make any diagnoses or treatment decisions since patients will be receiving Trueview scans in addition to their routine assessments. Appendix A contains a flow chart to describe the study sequence.

In Phase 2, the images collected on both the standard system and the Trueview software will be presented to a group of 2 independent radiologists for a structured, blinded assessment of image quality using the following criteria:

- Structure details
- Contrast
- Noise
- Ease of image review
- Overall summative assessment

A 3rd reviewer will be reserved for any major discrepancy in opinion persisting between the first 2 readers after consensus review of discrepancy cases (the consensus view comprising the final read result of the DR images)

The data from this assessment will be analysed by the statistics team at Factory-CRO according to the methods described in section 11. The methods for analysing the BMD measurements in phase 1 are also described in section 11. No image quality assessments will be conducted using the data from phase 1.

6.2. Comparators

6.2.1. Phase 1 – Dual Energy X-ray Absorptiometry (DEXA)

DEXA is widely regarded as the most commonly used method of reliably obtaining bone mineral density information, using X-rays to do so. Computed Tomography is also occasionally used. The site uses a General Electric Lunar system that is calibrated to provide BMD measurements that can be used for diagnosis of bone health conditions. The outputs from this system will be used as a direct comparator to the Trueview outputs.

6.2.2. Phase 2 – Digital Radiography

Digital radiography is a well-established imaging medium and all systems operate on the basic principle of using a digital X-ray detector to acquire an image based on X-ray photons passing through subject. The main difference between many systems is the way in which images are post-processed and purchasing decisions often come down to cost and the preferences in the way images are presented. For the most part, post processing does not necessarily change the diagnostic quality of the image and standard imaging protocols are used for specific body parts regardless of the system used.

In phase 2 of the study the standard set of exposures will be taken on a Siemens Ysio digital radiography system. This system has been chosen as it offers the flexibility to obtain the raw data required to assess the Trueview software and is commonly used at the site for the assessments the study will focus on.

6.3. Study Assessments

6.3.1. Phase 1

In phase 1, patients will attend the DEXA clinic for a BMD assessment from their hip (neck of femur). The results of this measure will be recorded along with the region of interest used for the calculation.

The patient will then attend the radiology department for a second assessment using the standard digital radiography system without an ASG. The radiography will aim to position the patient on the X-ray table in the same position as was used for the DEXA scan. Standard positioning is used in DEXA and cushions are often used to provide support. These same supports will be used in the digital radiography room to assist with positioning. The raw data will be saved and exported to the Trueview software and the region of interest will be selected by the radiographer to match that of the DEXA system, as detailed in the IFU. The resulting BMD measurement will be recorded.

The radiographers will extract the BMD from the Trueview output according to the protocol and will be blind to the BMD result from the DEXA scan to avoid any inadvertent manipulation of the data to be compared.

A daily calibration image will be collected to monitor potential system drift. This will involve the radiography department taking a single image of a medical calibration phantom on the Ysio DR system every morning. This information will be used to correct the Trueview BMD calculations should DR system drift be significant.

6.3.2. Phase 2

Phase 2 is broken down into low scattering and high scattering images. The procedure for acquiring the images differs in each case as in the high scattering case, an anti-scatter grid would normally be used.

The radiographer will be responsible for deciding whether an assessment will require a grid will follow one of two procedures depending on this decision. In the low scattering case, one set of images will be taken using the standard system operating procedure. Once this has been done, the raw image data will also be saved and exported to the Trueview software for scatter correction.

In the high scattering case, one set of images will be taken using the standard system operating procedure with an ASG in place. The radiographer will make a note of the X-ray tube settings defined by the automatic exposure control for this set of images. The ASG will then be removed and the X-ray exposure settings entered manually as those recorded in the first exposure. A second exposure will be taken and the raw image data will be saved and exported into the Trueview software for scatter correction.

In the event that repeat images are required during the standard care assessment, the patient will be withdrawn from the study and no further exposures taken for the purposes of assessing the Trueview device. It will be assumed that if a good image is acquired for the standard assessment, the settings used will produce a good image for the additional study assessment. No repeat imaging will be conducted for the study assessments. In all cases, images will be processed by the Trueview software, according to the instructions for use, after the patient has left the study.

All processed images will be transferred onto an encrypted portable hard drive and will be couriered to Professor Phil White at Newcastle University for the image quality assessment to be conducted. A dedicated viewing station consisting of a medical grade monitor and image viewing software, to be specified by Prof. White, will be supplied by IBEX for the image assessment process.

The independent radiologists assessing the images in Phase 1 will be presented with a randomised set containing both standard DR images and Trueview images. They will not know which method has been used to produce the images and will assess each image independently.

No two images from the same patient will be presented in any given set to eliminate the chance for the radiologist to recognise a particular patient and compare methods, thus the radiologists assessing the images will be blinded to allocation group.

6.3.3. Calibration

In addition to these assessments, it will be necessary to calibrate the DR system for the protocols to be used. The calibration process is a single procedure that can be conducted at the start of the study and does not involve any human participants.

The calibration process consists of taking a series of images of Perspex slabs at varying thickness levels using the settings for each of the imaging protocols to be used in the study. The process is described in detail in the IFU and will be conducted by a member of the investigation team following training by a Sponsor representative.

6.4. Participant Duration

Participants are only considered to be in the study for the time it takes from arriving for their assessment to the completion of their radiographic assessment. No patient follow-up is required and participation will be complete in a single visit. Screening and recruitment for both phases is expected to be complete within 5 months of study start. See Appendix A for a detailed study flow chart.

7. Clinical Investigation Population

7.1. Number of Participants

This is a single site, two phase study that will take place at the James Cook University Hospital, Middlesbrough. 130 patients will be recruited from the Rheumatology (DEXA) clinic for Phase 1 and 60 patients will be recruited from the orthopaedic outpatient's clinic for Phase 2.

Based on the high volume of patients attending both clinics, recruitment periods for Phase 1 and Phase 2 are both expected to be 3-5 months.

7.2. Inclusion Criteria

Patients who meet the following criteria will be considered eligible for Phase 1 of study:

1. Caucasian male or female, at least 50 years of age, attending for a DEXA scan of Neck of Femur (for measurement of bone mineral density);
2. Patient able to comprehend and sign the Informed Consent prior to enrolment in the study

Patients who meet the following criteria will be considered eligible for Phase 2 of study:

1. Male or female, 18 years of age or over, attending orthopaedic outpatient's clinic and requiring plain radiographs of wrist or shoulder or pelvis;
2. Patient able to comprehend and sign the Informed Consent prior to enrolment in the study

7.3. Exclusion Criteria

The participant may not enter the clinical investigation if ANY of the following apply:

Patients who meet the following criteria will NOT be eligible for Phase 1 of the study:

1. Women who are pregnant or are breastfeeding
2. Concurrent participation in another experimental intervention or drug study
3. Has an implant or other radio-opaque foreign body in the location of the assessment
4. Unwilling or unable to provide informed consent

Patients who meet the following criteria will NOT be eligible for Phase 2 of the study:

1. Women who are pregnant or are breastfeeding
2. Concurrent participation in another experimental intervention or drug study
3. Unwilling or unable to provide informed consent
4. Currently wearing a cast on assessment site that is not intended to be removed prior to radiographic assessment
5. Has an implant or other radio-opaque foreign body in the location of the assessment

8. Participant Selection and Enrolment

8.1. Identifying Participants

All patients who have scheduled appointments at any of the orthopaedic outpatient clinics or scheduled appointments for DEXA scans will be screened and potentially eligible patients will be sent study information by post prior to their appointment. Eligibility of participants will be confirmed during the clinic visit by designated research staff assigned to the study. Patients who meet the criteria described in section 7 will be approached to obtain consent as described in the following sections. Patients are considered enrolled once they have signed the informed consent form and leave the study once their radiographic assessments have been conducted.

8.2. Consenting Participants

The participant must personally sign and date the latest approved version of the informed consent form before any clinical investigation specific procedures are performed.

All patients who have scheduled appointments at any of the orthopaedic outpatient clinics or scheduled appointments for DEXA scans will be screened and potentially eligible patients will be sent study information by post prior to their appointment. Written versions of the participant information and informed consent will be presented to the participants detailing no less than: the exact nature of the clinical investigation; the implications and constraints of the clinical investigation plan; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the clinical investigation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed the time between receiving the study information by post and their attendance at the clinic to consider the information, and will have the opportunity to question the Investigator, members of the research team or other independent parties to decide whether they will participate in the clinical investigation. Written Informed Consent will then be obtained when they arrive at the clinic by means of participant dated signature and dated signature of the person who will present and obtain the informed consent. The person who obtains the consent must be suitably qualified and experienced and will have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the clinical investigation site.

If, at any point during the study, new patient information is produced, it will be sent out via post to all patients who have not yet had their appointment and also to those who have taken part in the study. It will not be sent to those who have had their appointment but did not enrol in the study.

8.3. Screening for Eligible Participants

Patient identification for both phases of the study will be conducted as described in section 8.1. Once eligible patients have been identified they will be provided with the study information and informed consent details prior to their visit. At the visit the following data will be collected.

8.3.1. Demographics

Patient year of birth and gender will be recorded. Race will be recorded only in Phase 2.

8.3.2. Medical History

Detailed medical history is not required. For Phase 1, data required for the completion of the FRAX calculation tool will be recorded. This includes details of:

- whether a subject or their parent has had a previous hip fracture
- whether they currently smoke
- whether they currently consume more than 3 units of alcohol per day
- whether they currently take prescribed glucocorticoid medication
- whether they have been previously diagnosed with rheumatoid arthritis or secondary osteoporosis (a disorder strongly associated with osteoporosis such as type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease

8.3.3. Physical Examination

Height and weight will be recorded. Standard procedures for radiology at the study site will be followed, including recording of last menstrual period where applicable.

8.4. Withdrawal of Participants

Patients are only participants in the study for the duration of the outpatient visit for the fracture or DEXA assessment. Participation ends once the radiographic assessments are complete.

Patients may choose to withdraw from the study following screening and consent up until the point at which the radiographic assessment using the Trueview software is conducted.

In standard radiography, it is standard procedure to retake a set of images if the exposure is considered to be inadequate. If this occurs during the collection of standard image sets for an enrolled patient when an ASG is used, they will be withdrawn from the study and no additional radiographic assessments will be made beyond those needed for the usual clinical care.

For all assessments in this study, the participant will be subject to additional exposure to ionising radiation which will be conducted using standard hospital equipment, after which their participation ends and they exit the study. It is only the subsequent processing of this data that will be done using the Trueview software. As such, it is not expected that any malfunction of the Trueview software would lead to the withdrawal of a patient.

8.4.1. Replacement of subjects

In the event that a patient is withdrawn from the study before radiographic assessments, they will be replaced by further recruitment using the procedures defined in sections 8.1 to 8.3 until the required number of patients has been reached.

Additionally, further recruitment will be conducted to account for patients withdrawn from the study due to requiring retakes of the standard radiographs.

9. Medical Device

9.1. Device Details

The device under review in this study is the IBEX Trueview software. It is a Class IIa medical device under the EU Medical Device Directive and will not be CE marked by the start of the proposed clinical trial.

9.2. Device Manufacturer

IBEX Innovations Limited
Explorer 2
NETPark
Sedgefield
TS21 3FF
UK

9.3. Device Accountability

The Trueview software is intended to be integrated into an OEM system however, for the purposes of this clinical study the software will be installed on a standalone computer that will be provided by IBEX. The computer will be supplied by IBEX and the study site will take responsibility for the duration of the study. At the end of the study, IBEX will collect the computer and resume responsibility.

- IBEX will keep a log of:
- the date of shipment
- date of receipt at the study site
- the computer asset ID and software version number
- the date of return to IBEX

- if applicable, shipment details of malfunctioning and repaired devices

9.4. Storage Conditions

The computer is to be installed in a secure room at the study site and will only be operated by investigation staff who have been trained to do so.

9.5. Concomitant Medications

9.5.1. Permitted medications

Throughout the clinical investigation Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care for Clinical Investigation Assessments

9.5.2. Prohibited medication

Not Applicable

9.6. Safety Assessments

A review of the radiation risk posed by the study has been completed and the risk deemed minimal. Following a thorough risk analysis of the Device, there are no residual risk that require any further safety assessments as the Device does not affect the normal operation of the standard radiography equipment and will not come into contact with the patient.

9.7. Clinical Investigation Assessments

The clinical study is split into two Phases that involve different patient groups. A representative from the sponsor may be present during these assessments.

9.7.1. Phase 1

Patients in Phase 1 will be recruited from the Rheumatology clinic and will be patients who are attending for a DEXA scan. These patients will receive their DEXA scan following standard procedures (which will include a measurement of BMD at the neck of femur) and will then be invited to attend the radiology department to receive an additional scan of the pelvis using a digital radiography system. Care will be taken to position the patient in the same way as they would be positioned for the DEXA scan. The raw data output from this assessment will be processed by the Trueview software to provide a bone mineral density measurement for comparison with that of the DEXA system.

Care must be taken to ensure patient positioning is as close to that of the DEXA scan and that the region of bone selected for the BMD measurement matches that of the DEXA system.

In both phases, patients will exit the study once their radiographic assessments are complete.

9.7.2. Phase 2

Patients in Phase 2 will be recruited from those patients who are attending an orthopaedic outpatient's clinics and would normally be receiving an X-ray assessment of their wrist, shoulder or pelvis.

In cases where no anti-scatter grid (ASG) would normally be used (i.e., for low scattering images), patients will have their set of X-ray exposures taken following the standard system operating procedures and will then exit the study. Raw data from the radiographic system will be processed using both the standard procedure and the Trueview software to produce the two sets of radiographic images used for assessment. In cases where an ASG (i.e., for high scattering images) is required for the standard exposures, two sets of exposures will be required. The first set will be taken following

standard procedures with the ASG in place. A second set will be taken without the ASG in place and raw data will be processed using the Trueview software. Both procedures result in a separate radiographic image which will be used for assessment.

In the event that repeat images are required during the standard care assessment, the patient will be withdrawn from the study and no further exposures taken for the purposes of assessing the Trueview device.

10. Data Collection

The standard procedures for handling and processing records will be followed as per ISO14155 and Factory CRO's Standard Operating Procedures.

10.1. Source Documentation

Source documentation will be maintained to capture the course of treatment and to substantiate trial data integrity. For current study, source documentation will include, but is not limited to, worksheets, hospital and/or clinic or office records documenting subject visits including study procedures and other treatments or procedures, medical history and physical examination information, imaging results and laboratory results and reports.

10.2. Case report forms

The investigators shall ensure the accuracy, completeness, legibility and timeliness of the data reported in the (electronic) Case Report Forms (eCRFs) and in all required documentation.

An electronic data capture (EDC) system with eCRFs will be used for this study. All eCRFs, will be completed in English. Subjects will be uniquely identified by a study subject number. If an item is not available or is not applicable, this fact should be indicated; no space is to be left blank. The principal investigator who has signed the protocol signature page or his/her authorized designee will personally sign the eCRFs to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner after the subject's visit.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF will be handled according to ISO14155 guidelines and shall be dated, initialled, and explained if necessary, and shall not obscure the original entry (i.e. an audit trail shall be maintained); this applies to both written and electronic changes or corrections.

10.3. Data retention

The investigator will maintain all study records for the minimum time required in the country in which the study is conducted. For the selected site in the UK this is specified as 15 years. Records to be retained may include: all correspondence, documentation of device receipt and disposition, each subject's case history and record of exposure to the device, the protocol and amendments, Investigator's Brochure, and dates and reasons for any protocol deviations or as otherwise specified by the applicable laws and regulations.

10.4. Subject confidentiality

Subject confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique subject identification code (Site number combined with subject number) will be used that allows identification of all data reported for each subject. A key to the subject code will be kept in the Investigator Site File, which is kept on site. This key will link the subject ID code to the subject's name and hospital ID number

and it is called the 'subject identification log'. The 'subject identification log' nor copies of this log will by no means leave the hospital site. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the subject's privacy is guaranteed.

Data Protection Consent and other documentation in accordance with the GDPR, relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrolment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements.

11. Statistics

The goal of this study is to assess the safety, image quality and bone mineral density accuracy of Trueview in wrist, shoulder and pelvis image locations using low- and high-scatter images. These parameters are assessed on adults requiring radiographic assessment.

11.1. Description of Statistical Methods

A detailed Statistical Analysis Plan developed prior to study completion and database lock will fully describe the statistical methods to be used. The analysis will consist of demographic data, safety data, image quality data and BMD data. Furthermore, data will be summarized with standard descriptive statistics and provided in tables, listings and figures.

Descriptive and hypothesis-testing approaches will be used to meet the protocol objectives. Quantitative variables will be described by category and overall using summary statistics with their 99% confidence intervals. Qualitative variables will be described by frequency and count by category and overall.

11.1.1. Phase 1 Primary Analysis

The primary statistical method will be the analysis of bone mineral density data using a paired means t-test. If the results of this test are statistically significant (p-value ≤ 0.01) then there will be evidence that the Trueview system has equivalent average BMD accuracy compared to the gold standard DEXA system at an equivalency limit of 0.08. Furthermore, they are considered equivalent if the paired means difference 99% confidence interval is above or below ±0.08 (LIM).

11.1.2. Phase 2 Primary Analysis

The secondary statistical method will be the analysis of the average image quality data using a paired means t-test. If the results of this test are statistically significant (p-value ≤ 0.01) then there will be evidence that the TrueView system has non-inferior average image quality compared to standard radiography at a non-inferiority limit of -0.3. Furthermore, TrueView is considered non-inferior if the upper limit of the paired means difference 99% confidence internal is at least -0.3 (NIM). This test will be repeated for each image location/scattering type, image criteria and overall.

For patients requiring retakes, as described in section **Error! Reference source not found.**, no Trueview images will be collected and therefore a comparison cannot be made. To describe possible bias, we will perform a sensitivity analysis at study end. This would entail performing an analysis without missing data and also with missing data as worst-case scenario. These will then be compared to determine if the missing data did have an effect and, if so, the size of the effect will be described.

11.1.3. Safety Analysis

An overall summary of AEs (defined in section 12) will be provided including the number of events and percent of subjects with any AEs, SAEs, and USADEs. For each type of event, the number of events and number and percent of subjects with the event will be provided in a table using the coded terms. Separate summaries of all adverse events will be summarized by relationship to device and procedure.

Laboratory results will be examined for trends over time and any clinically significant values for individuals will be reported. The safety endpoint will be analysed using the safety population. These analyses will be performed independently for Phase 1, Phase 2 and overall.

In addition, the reports (listings) and descriptive statistics (e.g. frequency and percentage) used to describe the safety outcome (adverse events, serious adverse events, etc.) will be reported for both the DEXA system and the Trueview software to determine if there are any differences. Relatedness to any of the DEXA or Trueview system will be added to the AE report forms. If there are no clinically significant differences in these analyses or if there are no AEs related to the DEXA and Trueview system, then Trueview will be declared non-inferior to the current standard. The same will be done for Phase 2, comparing AEs related to standard system vs Trueview.

11.1.4. Analysis Populations

Data analysis with respect to the primary and safety endpoints will be completed for two defined populations:

1. Safety Population: Population that is consistent with the Intention-to-treat principle, i.e. all enrolled subjects who received a radiographic assessment, including those whose first exposure was considered inadequate and would require the X-ray to be re-taken.
2. Per-Protocol Population: Enrolled subjects who completed the radiographic assessments and who did not have any major protocol deviations.

11.2. The Number of Participants

This clinical investigation is powered for two phases with all subjects recruited at a single site, James Cook University Hospital. Phase 1 will recruit from the Rheumatology (DEXA) clinic and phase 2 will recruit from the orthopaedic outpatient's clinic.

11.2.1. Phase 1

In phase 1 the sample size is powered to detect equivalence between the bone mineral density measurement provided by Trueview and DEXA.

Standard deviation for BMD varies between 0.069 and 0.156 (Sezer, et al., 2015). Assuming these same population variations occur within subjects then these estimates may be used for S_d.

In order to prove that Trueview agrees with DEXA to within the combined errors of both measurements we need to show that the difference between the Trueview BMD measure (after calibration on to DEXA) is within the quadrature sum of the errors from both measurements. From our own observations we have calculated this to be 9.19%

The LIM requires an estimate of the limit for which difference in paired values will be considered equivalent. Thus, if we used this estimate at the paired level, saying that if each paired difference was with 9.19%, we can estimate the LIM using (from Sezer) the BMD being between 0.82 and 1.30. If the BMD in Trueview is found to be 0.82 for a subject, then we would want the DEXA to be between 0.74 and 0.90 to consider it equivalent. Thereby, the paired difference limit would be within 0.08 (0.82-0.90, 0.82-0.90). However, if the larger estimate of BMD is found to be 1.30 for a subject then the LIM would be within 0.12 (1.30-1.42, 1.3-1.18).

Given the most unfavourable conditions presented here, a LIM of 0.08 and a standard deviation of 0.156 has been chosen as the basis of the sample size calculation.

With a dropout rate of 3% and a significance level of 1%, a sample of size 130 provides a 90% power to detect equivalency between Trueview and the reference standard.

11.2.2. Phase 2

In phase 2 the sample size is powered to detect non-inferiority between the average of reviewer's image quality scores for Trueview and standard radiography. Assuming that the Trueview will provide an image quality within 10% of that of standard radiography image quality and that in general, standard radiographs would normally be scored between 3-4, it follows that a standard deviation of paired differences of 0.3 and a non-inferiority margin of -0.3 would detect non-inferiority.

With a dropout rate of 3% and a significance level of 1%, a sample of size 60, equally split across the imaging regions (wrist, shoulder and pelvis) provides 90% power of detecting non-inferiority at each of those regions.

11.3. The Level of Statistical Significance

Statistical tests will use a significance level of 1%.

11.4. Criteria for the Early Termination of the Clinical Investigation

The Sponsor may choose to prematurely terminate the full clinical investigation if the medical device is found to be related to adverse events and/or serious adverse events. Prior to each new procedure the device history is checked for the occurrence of any untoward event providing grounds for early study termination including:

1. Any type of related AE
2. Any type of related SAE
3. Occurrence of any other event or condition, which in the view of the investigators could jeopardize the safety of the study participant or complicate interpretation of the safety data.
4. Any software errors recorded that may affect the integrity of study data

11.5. Procedure for Accounting for Missing, Unused and Spurious Data

Should the study be terminated early, the investigative team will discuss with the Medical Monitor the reason for termination and determine which protocol objectives can be addressed in an unbiased manner with the available data. The available data will then be analysed and interpreted.

If more than 1% of the data points are missing and are assumed to be either missing completely at random (MCAR) or missing at random (MAR), then multiple imputation will be used to impute and sensitivity analyses will be performed. If missing data are assumed to be missing not at random (MNAR), then the study will be declared invalid and no imputations nor hypothesis testing will occur.

11.6. Procedures for Reporting Any Deviations from The Original Statistical Plan

If deviation from the original statistical plan occurs after the final revision of the SAP, the CRO should report these deviations in the clinical study report (CSR). If there is intention to deviate from the SAP for primary, secondary and safety objectives, then these deviations must be defined before final analysis reporting, ideally in a revised SAP, and should be justified by statistical methodology. Other deviations should be presented as exploratory analyses.

11.7. Inclusion in Analysis

All eligible participants with completed radiographic assessments will be included in the analysis.

12. Safety Reporting

12.1. Definitions

12.1.1. Device Deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

Since the Trueview software is only used to process images once they have been taken on the standard hospital equipment, it will only be used once patients have exited the study. As such it is not anticipated that any device deficiencies will result in an adverse event, anticipated or otherwise.

When using ionising radiation, there is a risk that the standard digital radiography system in the hospital could malfunction and expose a patient to dangerous levels of ionising radiation, however these systems are now commonplace in most hospitals and designed to fail safe. Regular maintenance and inspection by regional medical physics groups ensures that systems are safe. As such, we do not expect any adverse events associated with the standard digital radiography equipment to occur.

12.1.2. Adverse Event (AE)

An AE or adverse event is:

Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a clinical investigation of a medical device, which does not necessarily have to have a causal relationship with the device under investigation.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.

The most likely AE that would arise in this study is that patients would receive additional X-ray dose over and above that budgeted for the standard care exposure plus any additional exposures defined in this CIP but not considered to be a significant risk to the patient. The anticipated dose budgets for the procedures to be conducted in this study are defined in Section 4.7.5.

Other AEs might include accidental physical harm caused to patients during positioning on the radiography system.

12.1.3. Adverse Device Effect (ADE)

All untoward and unintended responses to the medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

As the device does not have any effect on the treatment received by the patient, either in the collection of the radiographic images or in the assessment or diagnosis of any medical conditions, there are no anticipated ADE associated with Trueview.

12.1.4. Serious Adverse Event (SAE)

SAE is an adverse event that

- Led to death
- Led to foetal distress, foetal death or congenital abnormality or birth defect.
- Led to serious deterioration in the health of the subject that
- Resulted in a life-threatening illness or injury

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Resulted in a permanent impairment of a body structure or a body function
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

As above, the most likely SAE that would arise in this study is that patients would receive additional X-ray dose over and above that budgeted for the standard care exposure plus any additional exposures defined in this CIP and considered to be a significant risk to the patient. Although such an event would not likely present itself in any obvious patient symptoms at the time of exposure, it could be considered to contribute to the likelihood of developing future radiation induced cancers.

The anticipated dose budgets for the procedures to be conducted in this study are defined in Section 4.7.5.

12.1.5. Serious Adverse Device Effects (SADE)

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to characteristics of a serious adverse event.

SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances have been less opportune.

All cases judged by either the reporting medically qualified professional or the sponsor.

As the device does not have any effect on the treatment received by the patient, either in the collection of the radiographic images or in the assessment or diagnosis of any medical conditions, there are no anticipated SADE associated with Trueview.

12.1.6. Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature,

severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

12.2. Reporting of AEs

All AEs occurring during the radiographic assessments specified as part of the clinical investigation observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the clinical investigation plan.

The following information will be recorded: description, date of onset and end date, severity, and relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer. Serious Adverse events will be monitored until they are adequately resolved or until up to 30 days after subject study end.

All ADE that result in a participant's withdrawal from the clinical investigation or are present at the end of the clinical investigation, should be monitored until they are adequately resolved or until up to 30 days after subject study end.

Pregnancy is an exclusion criterion, however if the situation occurs that a patient was unknowingly pregnant at the time of study treatment, the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect. In addition, a protocol deviation should be recorded.

12.3. Timelines for Reporting all AEs and SAEs

The investigator shall notify the sponsor or its representative of any serious adverse events or serious adverse device effects within 24 hours upon becoming aware of the event, by completing a "serious adverse event" form in the eCRF and immediately updating it once new information become available. In case the eCRF is not available when the investigator became aware of the event requiring immediate notification, the investigator shall contact:

Factory CRO for medical devices
Prof. Brinkhorstlaan 10, Building 54
3723 MB Bilthoven
The Netherlands
+31 30 229 2727

As the nature of the device means that it is unlikely to result in an AE/SAE, only AEs reported during the patient involvement (i.e. during the time between enrolment and the completion of their radiographic study assessments) will be recorded. There will be no follow-up period beyond the end of the study.

12.4. Reporting of Device Deficiencies

All Device Deficiency data will be collected throughout the clinical investigation and will be reported to the Sponsor on a dedicated eCRF. Device deficiencies, that could have led to a serious adverse device effect will be reported as soon as possible but no later than 72 hours of first learning of the event.

12.5. Annual Reports

In addition to the expedited reporting above, the CRO shall submit once a year throughout the clinical investigation or on request a Safety Report to R&I, the Competent Authority HRA and Ethics Committee.

13. Clinical Investigation Management

13.1. Clinical Investigation Steering Committee

A separate steering committee is not required for this investigation as the responsibilities of a steering committee will be assumed by Factory-CRO, the contract research organisation managing the study. They are considered to be sufficiently independent of both IBEX (the Sponsor) and the investigation team at JCUH (the study site) to conduct these responsibilities without introducing any bias to the investigation.

13.2. Data Monitoring Committee

As this is a low risk study that does not involve children or vulnerable populations, an independent data monitoring committee (DMC) is not required. Safety reporting will be done as required per local legislations/regulations (see section 12 above), and monitoring will be performed by Factory CRO which includes review of safety events by a medical monitor.

13.3. Inspection of Records

Investigators and institutions involved in the clinical investigation will permit clinical investigation related monitoring and audits on behalf of the sponsor and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all clinical investigation records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all clinical investigation records and source documentation.

13.4. Clinical Investigation Monitoring

A Research Project Manager from CRO will visit the Investigator site prior to the start of the clinical investigation and during the course of the clinical investigation if required, in accordance with the monitoring plan. Monitoring will be performed according to ISO14155. Data will be evaluated for compliance with the clinical investigation plan and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the clinical investigation plan, ISO14155 and the applicable regulatory requirements.

A medical monitor who is an independent physician not participating as a clinical investigator in the clinical study will provide safety oversight for the study. Details of the medical monitor responsibilities, study review activities and sponsor reporting procedures are included in the Safety Data Handling Plan and include:

- Provide medical and scientific input to review clinical data, subject medical safety data and laboratory values;
- Maintain ongoing assessment of the safety profile of the investigational device during the investigation;

Provide medical surveillance and evaluation of Serious Adverse Events (SAEs) and unanticipated adverse device effects (UADEs).

13.5. Activities Performed by Sponsor Representatives

As the study sponsor, IBEX will be responsible for performing the following activities:

- auditing the study as required according to ISO14155:2011 and ensuring any exceptions are justified and documented
- training the investigation team on the use of the Trueview software for processing images and conducting calibration
- training of the CI in the Sponsor's procedure for reporting serious breaches of GCP as defined in ISO14155
- delivery of the standalone computer to the study site at the start of the study
- collection of the standalone computer from the study site at the termination of the study
- ensuring the CRO is fulfilling its obligations to conduct the study according this CIP and good clinical practice and their SOPs

14. Good Clinical Practice

14.1. Declaration of Helsinki

The Investigator will ensure that this clinical investigation is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2013, with additional footnotes added 2002 and 2004).

14.2. ISO 14155:2011

The Investigator will ensure that this clinical investigation is conducted in full conformity with relevant regulations and follow the standard for Clinical investigation of medical devices for human subjects - Good Clinical Practice (ISO 14155:2011).

14.3. Approvals

The clinical investigation plan, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval before initiating the clinical investigation.

The sponsor will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Participant Confidentiality

The clinical investigation staff will ensure that the participants' anonymity is maintained. The participants will be identified only by site number and a participant's ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by clinical investigation staff and authorised personnel. The clinical investigation will comply with the GDPR which requires data to be anonymised as soon as it is practical to do so.

14.5. Other Ethical Considerations

The study will not include vulnerable populations or children as eligible participants to ensure that those unable to provide their own well-informed consent or those who are particularly sensitive to the effects of ionising radiation are not able to take part.

If any additional requirements are provided by the REC or regulatory authority, these shall be implemented and followed fully.

14.6. Data Handling and Record Keeping

An EDC system with eCRFs, DF Discover, will be used for the purposes of this clinical investigation. The data entered into the DF Discover will be fully validated, using clinical investigation-specific range and consistency checks and database listings. Queries will be issued to the site via the EDC system, and are to be resolved by the principal investigator or their designee using the EDC system. An audit trail is available for tracking all information that the EDC user enters, modifies or deletes.

The participants will be identified by a clinical investigation specific participant number and/or code in any database. The name and any other identifying detail will NOT be included in any clinical investigation data electronic file.

Data validation will be completed on a regular basis. The entire database will be re-validated to ensure that there are no outstanding data discrepancies prior to database lock. Any changes to the database after that time will require written agreement by IBEX.

15. Clinical Investigation Conduct Responsibilities

15.1. Clinical Investigation Plan Amendments

Amendments to the clinical investigation plan must be approved by the Sponsor before submitting to the appropriate REC, Regulatory Authority and local R&D for approval.

15.2. Clinical Investigation Plan Violations, Deviations and Serious Breaches

The CI will not implement any deviation from the clinical investigation plan without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to clinical investigation participants.

In the event that the CI needs to deviate from the clinical investigation plan, the nature of and reasons for the deviation will be recorded in the CRF and notified to the Sponsor within 72 hours. If this necessitates a subsequent clinical investigation plan amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, Regulatory Authority and local NHS R&I for review and approvals as appropriate. It is Sponsor policy that waivers to the clinical investigation plan will not be approved.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately.

15.3. Corrective and Preventative Actions and Investigator Disqualification Criteria

If a serious breach is suspected, the PI will complete a “Corrective and Preventative Actions Report” and submit it to the Sponsor. The report will provide:

- a description of the finding along with immediate actions taken to mitigate the breach
- categorization of the finding according to criteria detailed on the report template (critical, major or other)
- suggested corrective actions to be implemented following the breach
- suggested processes to be implemented to prevent a repeat of the breach
- expected date for the implementation of corrective and preventative actions related to the finding

In the event that a corrective or preventative action requires an amendment of the CIP, the process described in section 15.1 should be followed.

If a serious breach of GCP is directly attributable to the PI, they will be considered by the sponsor for disqualification from any further participation for any of the following criteria:

- the breach is categorized as major, as per the definitions in the reporting template
- corrective and preventative actions have not been implemented adequately or within an acceptable timeframe

If the PI is disqualified, the study will be suspended until a replacement is identified.

15.4. Temporary Suspension

The study may be temporarily suspended where necessary in the event of:

- A serious breach of GCP, such as major deviation from the CIP
- A device is defective and cannot be immediately replaced
- An investigator withdraws from the study and cannot be immediately replaced
- An investigator is disqualified from further participation in the study

In these cases, the temporary suspension will be lifted once IBEX has concluded an analysis of the reasons for suspension and is confident that the required corrective and preventative actions have been implemented. Once the decision to resume the study has been made, IBEX will inform the CRO who will inform the ECs, PI and relevant regulatory authorities and the temporary suspension will be lifted.

15.5. Clinical Investigation Record Retention

All applicable clinical investigation documentation, as defined by ISO 14155 Annex E, will be kept for 15 years from the clinical investigation plan defined end of clinical investigation point. When the minimum retention period has elapsed, clinical investigation documentation will not be destroyed without permission from the sponsor.

15.6. End of Clinical Investigation

The end of clinical investigation is defined as the last participant's last visit.

The Investigators and Sponsor have the right at any time to terminate the clinical investigation for clinical or administrative reasons.

At the end of the clinical investigation, be it a natural or early termination, the following close-out activities will be conducted by the CRO.

All study records will be reviewed, including:

- completing all essential study documents
- completing all CRFs
- resolving any outstanding queries
- documenting the current status of all ongoing AEs
- making arrangements for archiving and record retention
- disposition of any other clinical investigation materials

The end of the clinical investigation will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the clinical investigation is terminated prematurely.

A full Clinical Study Report will be produced by the CRO detailing all aspects of the delivery of the study including, methodology and design and any deviations from the CIP; a statistical analysis of results and subsequent findings.

The clinical study report will be provided to the REC and Regulatory Authority within 1 year of the end of the clinical investigation.

15.7. Insurance and Indemnity

IBEX has clinical trials insurance limited to £5,000,000 in any one occurrence and in the aggregate during the study duration. This insurance is provided to IBEX by Nucleus Underwriting on behalf of Berkshire Hathaway International Insurance Limited under policy number CCZCPL17AA/AB/AI/AF-NUW01-10733.

15.8. Funding

The study is funded by IBEX Innovations using grant funding provided by the European Commission under the Horizon 2020 SME Instrument programme, grant number 777835.

IBEX will use this funding, along with its own funds as necessary, to ensure all financial obligations relating to the study are met.

16. Reporting, Publications and Notifications of Results

16.1. Authorship Policy

The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement. On completion of the clinical investigation, the clinical investigation data will be analysed and tabulated, and a CSR will be prepared in accordance with ISO 14155 guidelines. The CSR will be submitted to the Investigators, Ethics Committees and appropriate regulatory authorities. The authorship order will be decided jointly between the CI and the sponsor.

16.2. Publication

The results of this study will be published in 2-3 established journals and will also be disseminated through conference attendance with a budget of ~£3k per publication/conference.

Publications will follow ICMJE (ICMJE, 2018) criteria for authorship and all collaborators will be named in the acknowledgements.

17. References

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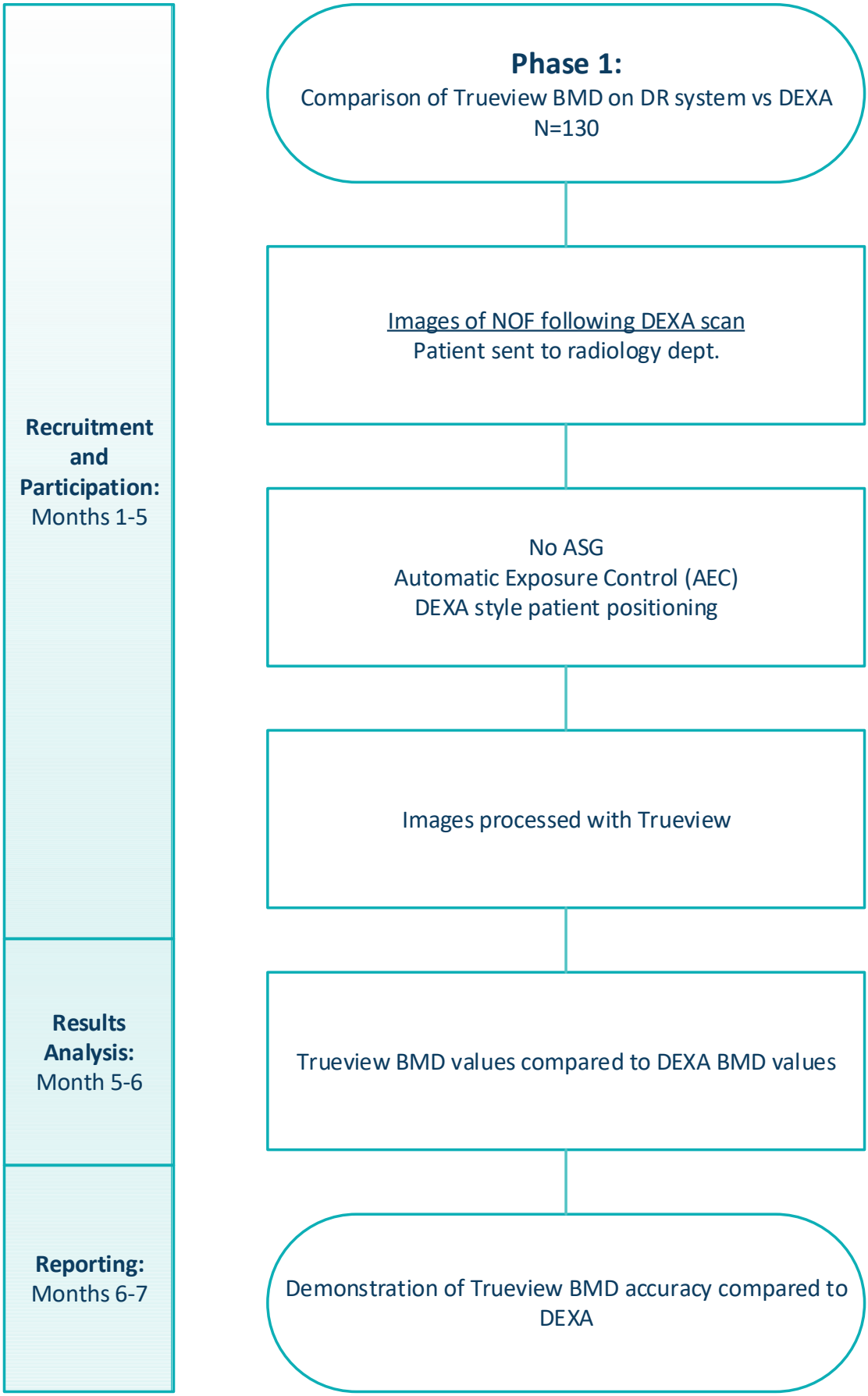
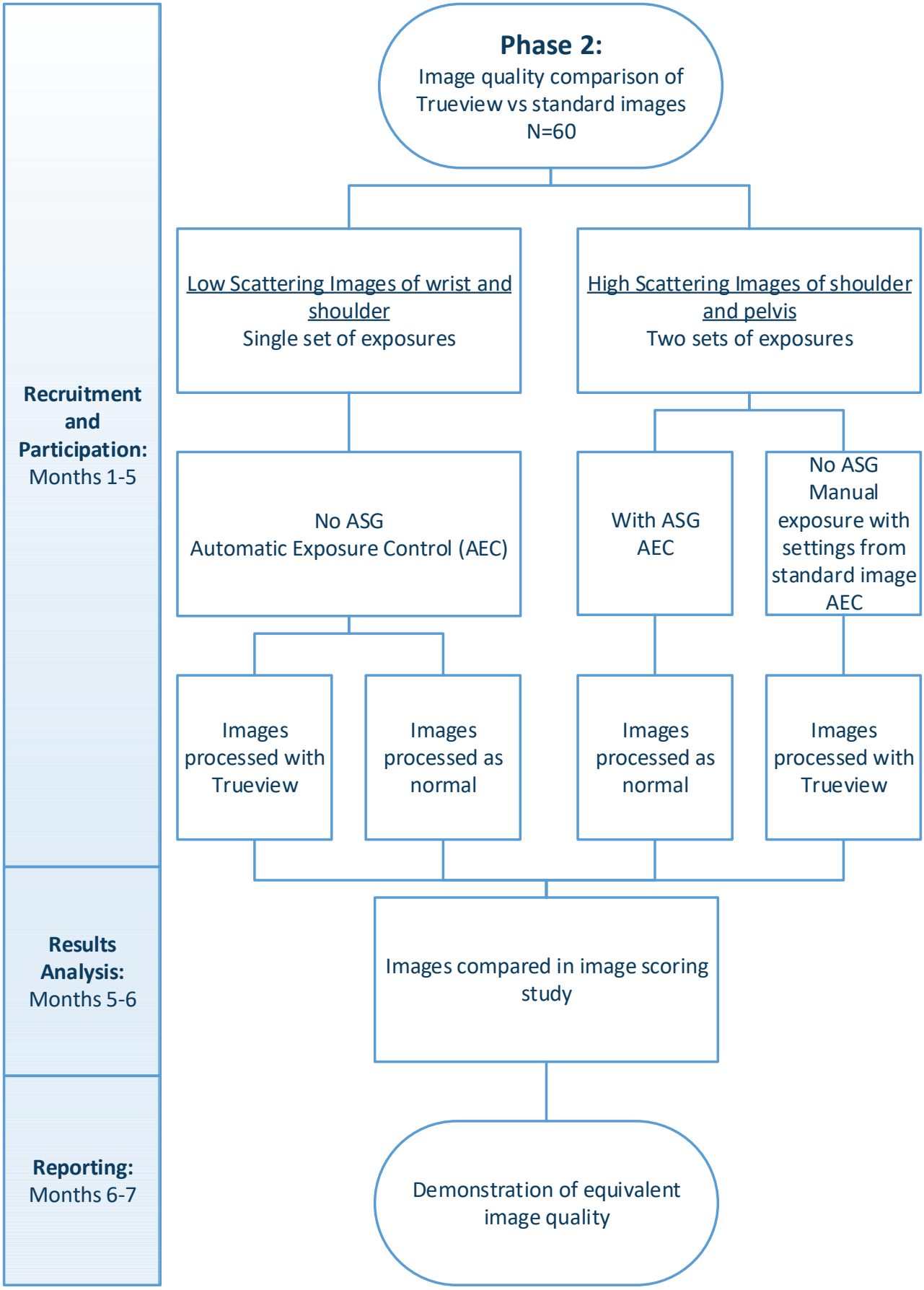
Appendix A. Clinical investigation flow chart




Recruitment and Participation: Months 1-5
Results Analysis: Months 5-6
Reporting: Months 6-7
Phase 2:
Image quality comparison of Trueview vs standard images
N=60
Low Scattering Images of wrist and shoulder
Single set of exposures
High Scattering Images of shoulder and pelvis
Two sets of exposures
No ASG
Automatic Exposure Control (AEC)
With ASG
AEC
No ASG
Manual exposure with settings from standard image AEC
Images processed with Trueview
Images processed as normal
Images processed as normal
Images processed with Trueview
Images compared in image scoring study
Demonstration of equivalent image quality

Appendix B: Clinical Investigation Contacts

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